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Society of University Surgeons

THE UNIVERSITY SURGEON

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THE subject of this address is the University Surgeon. I propose to examine the individual who makes up this organization, not as he is, of course, since human frailty besets the very best of us, but as he should be. Is he a university surgeon because of his native attributes and training or does his university connection or his membership in this Society confer upon him a unique distinction? What stamp of surgeon is he? What are his obligations and responsibilities? I realize that this is a formidable inquiry, and it is presumptuous of me to undertake it. Before doing so, therefore, let me digress for a moment and review with you the origins and purposes of this Society. It is appropriate to do so because they have a direct bearing on the principal subject of this address. Moreover, fifteen years have passed since the founding of this Society, and many of the new members may not be completely familiar with the original concepts of the Founders Group.

The idea which led to this Society was conceived in the mind of our first president, Samuel Stabins, of Rochester, New York. There were many others, I am sure, who had similar ideas, but Dr. Stabins had the conviction and determination to bring his idea into the open, and he had the great good fortune to have as his chief Dr. John Morton, who provided the necessary support without which the idea could never have germinated. At this point I would like to pay tribute to Dr. Morton, as foster father of this Society. Not only was he an influential factor in establishing the Society of University Surgeons, but his perennial presence at our meetings (characteristically sitting with Dr. Edwin Lehman, who deeply regretted that he could not be with us this year) has been a source of the greatest stimulation and happiness for all of us. It is singularly fitting, therefore, that we should have returned to Rochester for our fifteenth anniversary meeting, and it is most appropriate that we honor Dr. Morton as a great university surgeon.

Presidential address, presented at the Fifteenth Annual Meeting of the Society of University Surgeons, Rochester, New York, Feb. 12, 1954.

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The organizational meeting of the Society of University Surgeons was held on Feb. 28, 1938, in New York City. The following men were present: Dr. Stabins of Rochester, Dr. Finney of Johns Hopkins, Dr. Foster of Yale, Dr. Glenn of Cornell, Dr. Rousselot of Columbia, Dr. Stevenson of Cincinnati, and Dr. Zollinger of Harvard. I have written to each of these men, asking for their recollections of the meeting. As might be expected, the most complete answer came from the prime mover in the organization, Dr. Stabins, and with his permission and yours, I should like to read his letter.

Rochester, New York
September 12, 1953

Dear Bert:

To the best of my recollections this Society was first thought of about ten months before the meeting of the Founders Group at the New York Hospital in February, 1938. Prior to this meeting I had discussed the problem of the Resident Surgeon with Dr. Morton, who was in agreement that an active Surgical Society made up of men who were university trained should be organized. This was in the late spring of 1937. I went down to New Haven and discussed it with Dr. Harvey who likewise felt that there was need for an active Society of university trained surgeons. We were in disagreement in that he felt that all residents of university status regardless of what they did or where they went should be eligible. It seemed to me the Society would become so colossal that we would be in fact a Junior American College of Surgeons. It was my feeling that active membership should be limited to the age of 45 years, and that the Society should encourage well-trained men who were too young for admission to some of the older societies to meet on a common footing. I asked Dr. Morton to write to a number of professors of surgery, requesting that each name a delegate for an exploratory meeting to be held in New York. Upon favorable response of this request, I contacted Frank Glenn, who was Dr. Heuer's delegate, to arrange for a meeting at the New York Hospital. This resulted in the meeting of the Founders Group.

It was an informal meeting with many suggestions, and if memory fails me not, Bob Zollinger brought with him a draft of what he thought the Society should stand for. It was symbolic of what was to follow as the Society matured. It was torn to shreds after a few moments of discussion! The group were in accord that it should be a young men's society with an active age limit of 45, and that Resident Surgeons of accepted University Hospitals should be eligible for membership after they had held a teaching appointment in a University Hospital following the completion of their residency. It was agreed that the first meeting of the Society should be held at Rochester, New York.

This took place in February, 1939, with three more schools represented: Washington University by Frank Walton, Chicago by Alexander Brunschwig, and Vanderbilt by Cobb Pilcher. It was a good organizational meeting. The Constitution and by-laws were adopted. I was elected as first president. The scientific program was excellent and as we were comparatively small in size, everyone became well acquainted. Frank Walton bought champagne for the entire Society!

The following year we met at the New York Hospital. My presidential address was entitled "The Resident Surgeon" in which I attempted to trace, step by step, the evolution of residency training from the days of Halsted. Walton asked for my only copy, as he wished to publish it in the Washington University Quarterly. To this date it has not appeared. I suspect it met with foul play in transit from New York to St. Louis. From there on I believe the minutes of the meetings have been recorded, and you are fully aware no doubt of the "hills and dales" over which we bounded during the subsequent years. What I have omitted, I trust will be supplied by the other members of the Founders Group.

(signed)
Sam

The replies from the other members of the Founders Group were written in the same vein and were confirmatory. It is clear that they intended this to be an organization of young surgeons—I emphasize both *youth* and *surgery*—who would devote themselves to teaching and research. There is also a strong vein of camaraderie and friendship which runs not only through the letters which I received from the Founders Group, but also through all the correspondence and communications of the Society. I would not wish to place any emphasis on the significance of convivial relaxation as a catalyst for the development of great organizations, but the observations of Bernard De Voto may be applicable. In that delightful collection entitled *The Hour* he reflected on the failure of certain nations to "meet the challenge on which, as Mr. Toynbee has pointed out, their hopes of civilization hung." The American Indian was doomed because he regarded corn as a mere food, whereas the American Nation has reached the stars because "they knew what to do with corn."

I do not believe that Mr. De Voto or Mr. Toynbee would find this Society wanting! The record speaks for itself. Not only has the Society been a stimulating forum for the exchange of ideas among young surgeons engaged in teaching and research, but also as it matures it is having a significant influence on the broader aspects of American surgery. There can be no doubt that this Society has favorably influenced and contributed to residency training in this country. The report of the Committee on Postgraduate Education on the Effect of Pre-paid Insurance on Surgical Training is regarded as a classic analysis of a serious problem, and it is significant that the vast majority of professorships of surgery in this country are held by active or senior members of this organization. One word of warning here: It is of the greatest importance that as this Society matures it remain a young man's society. The senior members must come for the ride and to listen and learn rather than to pontificate. In this connection I hope we shall soon see a revision of the Constitution which will limit the right to vote to the active members. Since I shall be a senior member at the next meeting, this is my last chance to pontificate. I hope you will bear with me.

Who or what is a university surgeon? I must admit the species varies somewhat, and the casual and superficial observer is easily misled. He might be tempted to classify the surgeons found in university hospitals into three general types: "The Super Scientist," "The Brilliant Technician," and "The Old Dr. Chips." Although not holding to this view, I am impelled to call these broad categories to your attention.

The superscientific surgeon is the most prominent breed today. Some regard him as a scientist as well as a surgeon. Others, I am sure, think of him as a scientist rather than a surgeon. It is said that he is better qualified to study the enzymes in liver slices of the rat than to remove the appendix of a cat. There are subdivisions of this type. One of the less common, but more annoying, is the "Employment of the New Drug Division." He is likely to accost you in the midst of a purely social occasion and ask, "What are your results following the use of V-X 275, the new sympathomimetic liaphilizing decorticator that Hornquest has been playing with for the last ten years?" Since you have never heard of this agent, nor of Hornquest, you are forced to swallow suddenly,

cough slightly, pretend you did not hear him, and scurry to another part of the room. There are many other subdivisions, such as the "Isolated Gastric Pouch Collector," and the "Heavy Water or Isotope Metabolizer," but time does not permit me to discuss these in detail. Precocious phases of the Super Scientist are manifested by a knowledgeable stare and an impecunious appearance. Baggy trousers, a frayed shirt collar, and a "monitor badge" pinned to the lapel of a ragged laboratory coat all indicate that there are beta particles being emitted from the hypothalamus!

Now, I would be the last to decry the importance of fundamental research, but it is vital for men working in these fields to realize that their work becomes important to surgery only when it becomes intelligible to surgeons. It really is meaningless for the "fundamental research worker" to slip into the surgical ward to make certain chemical or physiologic determinations apart from the totality of the surgical care of patients. Whether it is the opsonic index of Wright or the eosinophil test of Thorn, its value and its permanence as a surgical tool can be determined only by the surgeon who understands surgery.

I am not condemning investigation or the continuous search for new knowledge. I am merely suggesting that just because it seems to be a new idea or has been "proved in the laboratory," it should not be accepted as gospel. Fundamental contributions to surgical care are like technical advances in any field. Advances in metallurgy can lead to better and stronger and lovelier bridges only when they are understood and applied by engineers who build bridges. The development of the jet engine became a useful military tool only when it could be made to fly a plane and the operation of that specific type of plane was integrated with the strategic and tactical phases of war. Even the atomic bomb would require the mind of a military strategist, not a physicist, for its use. Although we have not yet acquired an atomic bomb in surgery, when it becomes available, surgeons, not research workers, must use it, because the strategic and tactical phases of the care of surgical patients are as complex as any military operation. The "battle is the pay-off," and the clinical surgeon will always be at the front.

The second type of surgeon one may encounter in university hospitals is the "Brilliant Technician." This is the man who can remove five viscera with one hand tied behind his back quicker than you can remove half of one with all the resources of a six-man team. He has something in common with the successful lithotomist of earlier years. Although he is nervous about his prestige when confronted with the onslaughts of the superscientists, he is inclined to brush them off on the grounds that if you operate fast enough there is not time for sodium to move in or for potassium to move out of the cell. Like the spectators in the stands, they are fixed. Frozen in admiration!

The "Brilliant Technician" will sit down to breakfast with you and within five minutes will be describing the éclat with which he performed for the 439th time the same operation. There is an impressive subdivision of this group known as the "Cardiac Elites." I am not referring to that small number of distinguished individuals who in recent years have cracked the

frontiers of cardiac surgery. I am thinking of the host of enthusiasts to whom the heart now offers a rich pasture for technical exploration. Here again, such explorations have meaning only when applied to man as carefully and judiciously as the great pioneers of cardiac surgery did initially. There is no field today where a moral and ethical sense of what can be done and what should be done is so necessary.

There is one other difficulty with the "Brilliant Technician" and that is his obsession with numbers. Two thousand is so much more significant than 200. Twenty is of no significance to him whatsoever. Yet, I will venture the opinion that, for the most part, in the practice of surgery if twenty doesn't settle the matter, 2,000 will not either. It did not take twenty divisions of the patent ductus arteriosus to know that it was a good operation. And after twenty portacaval shunts it was evident that it was not quite as good! Two thousand are not going to make it any better.

The third type of university surgeon is the "Old Dr. Chips." He can neither operate nor do research. He is referred to as a "great clinical teacher." He is alleged to be the backbone of every department in the country, but his rank in the academic hierarchy rarely permits him a vote at faculty meetings. You can see this man hanging around the dressing rooms and corridors amid his heavy teaching schedule, looking for some neophyte whom he can collar and berate about the surgical amorality of the present generation. He emphasizes the personal touch in surgery, the importance of kindness and understanding in dealing with patients, and the fundamental value of the "sound clinical approach." There is nothing the matter with "Dr. Chips," except that he should never have gone into surgery, and because he himself is not a well-rounded surgeon, he weakens rather than strengthens the very precepts which he is championing. And I regret to say that at the present time here and there in teaching hospitals in this country, more "Dr. Chips'" are being guided and shielded to the completion of the "board certifications." Are we doing all we can to eliminate from surgical training the fine persons and capable minds who lack the temperament and technical competence to become able surgeons? It is a hard thing to do, but it is one of the responsibilities which university surgeons must shoulder. And are we as university surgeons doing all we can to support the principles of which, all too often, "Dr. Chips" is the lone defender? This is not a hard thing to do, but it is a responsibility which university surgeons as a group have not adequately shouldered.

If you are worrying about how to fit yourself into this classification, be relieved! When seen from a distance, each or all of these categories seem to merge into what I shall call the "As-Seen-From-The-Foot-Of-The-Ladder" type, and I suppose it is fair to say that as the mean age of this Society increases, there will be more of "Dr. Chips" in all of us!

I can best describe the "As-Seen-From-The-Foot-Of-The-Ladder" type by recapturing my own earliest impressions of university surgeons as I saw them coming to the Peter Bent Brigham Hospital to visit, teach, or serve as

surgeon-in-chief pro tem. I cannot say that the junior intern of today sees anything like this, but I presume it is what members of this Society hope he sees. I remember Drs. Fred Coller, Allen Whipple, I. S. Ravdin, Merle Scott, and many others. They all seemed to me to be wonderful men, self assured, confident, full of an extraordinary knowledge of the laboratory as well as the clinic, fine teachers, competent although not always brilliant technicians, and above all, interested in and considerate of young men. I must say they all possessed an extraordinary capacity for convivial relaxation too. Neither Mr. De Voto nor Mr. Toynbee could find them wanting! Supposedly they had everything, just the right amount of science, technical ability, and Dr. Chips. Of course, this is what we all strive for and, within the limits of our respective abilities, attain, but is this the essence of a University Surgeon?

It was not by accident that the word "university" was used in selecting the name of this Society. There was considerable discussion and controversy about it. Some felt that it might be misleading or even offensive to surgeons who were not actively engaged in university work. Others felt it was the only way to express in a single word the aims of the Society. It was a happy choice, and in concluding this address I shall attempt to define its significance in relation to surgery.

It is quite impossible to define the use of "university" as an adjective without considering the noun. Obviously the word cannot be divorced from the basic idea and function of a university. There is not the time, nor do I have the capability, to consider this subject in detail, but one or two definitions which have been made by others are appropriate. I have always been partial to Cardinal Newman's definition of a university as "an assemblage of learned men, zealous for their own science and rivals of each other, brought by familiar intercourse and for the sake of intellectual peace to adjust together the claims and relations of their respective subjects of investigation. They learn to respect, consult, and to aid each other. Thus is created a pure and clear atmosphere of thought." It has been said that Newman, when he wrote his "Idea of a University," was unaware of the value of research, but this is not so, because elsewhere he said: "It is a matter of primary importance in the cultivation of those sciences in which truth is discoverable by the human intellect that the investigator should be free, independent, and unshackled in his movement. Unless he is at liberty to investigate on this basis and according to the peculiarities of his science, he cannot investigate at all." And again, speaking of scientific investigators, "Great minds need elbow room: If you insist, that in their speculations, researches, or conclusions in their particular science that they must get up all that divines have said or the multitude believed upon matters, you simply crush and stamp out the flame within them, and they can do nothing at all."

Whitehead's definition is also to the point. He said: The function of a university is "the imaginative acquisition of knowledge." And of research, which he would begin at the moment a pupil undertakes the study of any science, he wrote: "The pupils should see for themselves, and experiment for

themselves, with only fragmentary precision of thought. The essence of the importance of science, both for interest in theory and for technological purposes, lies in its application to concrete detail, and every such application evokes a novel problem for research. Accordingly, all training in science should begin as well as end in research, and in getting hold of the subject-matter as it occurs in nature." If we admit to there being any science in surgery, is not every patient and every operation a potential "novel problem for research"? And should not surgical research begin with the patient and end with the patient regardless of how many laboratory steps may be required to complete it? If it does not begin and end with the patient, how can we call it surgical research? I am not decrying the value of pure research, but research for its own sake is the province of the basic sciences. It is an error to move a brilliant investigator in physiology or physical chemistry into the department of surgery unless he is willing to do utilitarian research. Such men may be valuable bridges between departments, but once they become so, their "ivory tower" is demolished. Such men are most valuable in their "ivory towers" doing the research which will open up entirely new vistas tomorrow. If the basic sciences are not five years ahead of the departments of medicine and surgery, we are losing ground.

The university surgeon must be in search of new knowledge, and he must be willing to learn, to acquire, and study in his own field the ideas and developments which are especially accessible to him in the atmosphere of a university. This is why the surgeon and the physician and the physiologist and the pathologist and the microbiologist and all the minds that make up a university must "respect, consult, and aid one another." If they do not do so, the very idea and function of the university will not be realized. This is just another way of saying that there should be no barriers between departments. Unfortunately, there are some educators today who would so scramble appointments to professorial chairs that there would be no departments behind the barriers!

So much for the word "university." What of the word "surgeon"? It is certain that the founders of this Society intended that it should be a society of men who understand the total care of surgical patients including the competent execution of surgical operations. But need the university surgeon be a surgeon, or is it enough to be a superscientist or a Dr. Chips? This is a moot point. Remember that Harvey Cushing once said that he hoped one day a university would appoint as professor of surgery a man who had no hands. And there can be no doubt at this moment that men with particular talents in the basic sciences and with research projects calculated to attract the money of grants appear especially desirable to committees charged with the task of selecting individuals for chairs of surgery.

It is my considered opinion, and I hope it reflects the body of opinion of this Society, that unless university surgeons in general and the professors of surgery in particular are actually capable surgeons, the whole structure of American surgery is threatened with collapse. How can the professor of surgery

contribute his respective share to the total atmosphere of a university if he is not a surgeon? It is preposterous to have him be a chemist or a microbiologist or a physicist. This would be destroying the department in order to bridge the barrier!

The professor of surgery must attempt to understand or seek consultation in or be helped with an infinite number of basic scientific developments, but unless he himself is a surgeon, how can he bring this knowledge to bear intelligently in his own field? The surgical care of the patient is the pay-off, and the professor of surgery must be a master of its tactics and its strategy. He will fail utterly if he does not constantly seek out, apply, and carefully appraise new scientific developments. If he is among the gifted few who can make fundamental observations and integrate them into the practice of surgery as well, so much the better. There are several such men in this Society. The universities who have them are fortunate, for they are rare.

However, if a man is capable of brilliant research in a basic field but really quite unqualified by temperament or ability to integrate this work in his daily practice of surgery, let him be a worker in that basic field. It is foolish to make him an unhappy professor of surgery. Conversely, if a man is a brilliant technician but unwilling to accept the responsibilities of teaching and to undertake the appraisal and utilization of new methods except as he can decipher them in terms of thousands of cases, let him be a surgeon. He may be a great surgeon, but he cannot be a University Surgeon.

If the professor of surgery is not able to appraise and interpret new knowledge in his own field, who can? This is a fundamental part of his primary mission which I am still naïve enough to believe is the *teaching of the principles and practice of surgery* to young men, most of whom are going to be surgeons, and only a few of whom will choose to be university surgeons. If the professor of surgery is not a surgeon and cannot be charged with the teaching of surgery, who can be so charged? Certainly not Dr. Chips.

Furthermore, there is a frightful responsibility and obligation to the patient which the professor of surgery cannot avoid. All of his teaching and research are of necessity affected by it. It is impossible to teach the practical aspects of surgical care without orientation to the patient as a person and a human being, not as a "cancer" or a "burn problem." The psychiatrist alone cannot teach this orientation. Dr. Chips cannot do it. The understanding of the human personality with respect to surgical care must be taught by the example and precepts of the professor of surgery. This is a grave responsibility, and he cannot shirk it. After all, is not his mission the better surgical care of the sick in all its ramifications?

Likewise in his research the university surgeon is by the very nature of things limited in what he can do. It is quite all right for Newton to drop an apple to demonstrate the law of gravity, but the professor of surgery cannot drop a patient out of a window to demonstrate the metabolic response to injury. I need not dilate on this point. The implications are obvious and

the laboratory is the essential steppingstone. But here again the professor of surgery must be able to bridge the gap between the patient and the laboratory. I do not believe he can do so unless he is a surgeon because if surgical research does not begin with the patient and end with the patient, it is simply not surgical research, however brilliant it may be.

The admonitions of Benjamin Brodie to the students of Bart's in the 1840's are as applicable now as they were then. He was speaking of matters which pertain to surgery in general of which the student must not lose sight, if he is to become an accomplished surgeon. He said, and I quote:

"An accomplished operator! That term may be used in various senses; but I will tell you, before I proceed further, in what sense I use it. I apply it, not to him who looks at his watch to see in how short a space of time an operation may be completed; nor to him who, during an operation, is putting himself in the situation of those who are looking on, considering what they will say, and anxious to appear dexterous in their eyes. According to my notions, he only is an accomplished operator who, before he engages in an operation, looks at all the consequences, both good and bad, which may ensue; and earnestly endeavors to lay his plans so that there may be as great a chance as possible of the former being obtained, and of the latter being avoided; and who, while actually engaged in an operation, thinks neither of himself nor of the bystanders, nor allows any question to arise in his mind except as to what he should do to bring the case ultimately to a safe termination with the least possible distress to the patient.

"Let me exhort you never to slur over a single case, nor proceed to the smallest operation without having well considered what accidents may happen, what evil may follow, what degree of danger may ensue. . . ."

The university surgeon of today can be no less accomplished in his care of the patient and in his "imaginative acquisition of knowledge" for the better care of the patient.

I have tried to indicate in some measure the real meaning of the term "University Surgeon." It is not something which is created by marble walls, isotope laboratories, volume of surgery, *ad hoc* committees, or membership in this Society. It is more fundamental than any of these trappings. A university surgeon can be found wherever surgeons of sound clinical background are willing to engage in the "imaginative acquisition of knowledge" and to "respect, consult, and aid" their colleagues in other scientific disciplines. Indeed, the right men can create "a pure and clear atmosphere of thought," although they may not be identified with what has been called a "recognized university hospital," a fact which I hope over the years this Society will take into consideration in its selection of new members.

THE HEALING OF THE DISRUPTED AND RESUTURED WOUND

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INTRODUCTION

THE pattern of healing in the resutured wound has been the subject of considerable study and some controversy. The excellent healing of an abdominal wound following dehiscence in man is a common observation. However, surgeons are loath to accept the idea that a resutured wound may heal more rapidly than a primary one. Botsford[1] and later Williams[2] have observed that during the first seven days the tensile strength of a resutured wound in the experimental animal is uniformly stronger than that of a primary wound. Sandblom[3] has reported that a separate wound made fifteen to twenty-five days after an initial wound and at a point some distance away in the body will heal more rapidly than normal. He postulated that anabolic processes set in motion by the initial wound hasten the healing of the second wound. Taffel[4] could not confirm the observation of Sandblom, and we likewise have failed to demonstrate a favorable influence of one wound upon another made at a fifteen-day interval at some other site in the body. On the other hand, if a fifteen-day wound which presumably has completed its healing cycle is reopened and resutured, the tensile strength of the resutured wound when tested on the third day is regularly stronger than that of a three-day wound in control animals.[5]

The present study is a further exploration of this observation in which some properties of the resutured wound are defined and some of the factors which may be responsible for the more rapid healing are appraised.

METHOD

White male rats of the Hisaw strain weighing between 180 and 220 grams were used. All were maintained on a diet of Purina rat chow and water ad libitum.

The standard test wound was a 4 cm. left rectus laparotomy incision made under sterile conditions after preparation of the shaved skin with Zephiran 1:1,000 solution. Ether anesthesia was employed. The wounds were closed with interrupted sutures of No. 32 stainless steel wire. The sutures were removed before determining the tensile strength, which was done in a manner previously described.[5] Briefly the technique consists of increasing the tension on the wound by infusing water into a plastic bag suspended by a

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heavy silk thread from the edge of the wound (Fig. 1). The opposite edge is held stationary. The weight of the bag and the water at the time of wound disruption is taken as the tensile strength. After testing, the wound may be resutured and then retested at a later date.

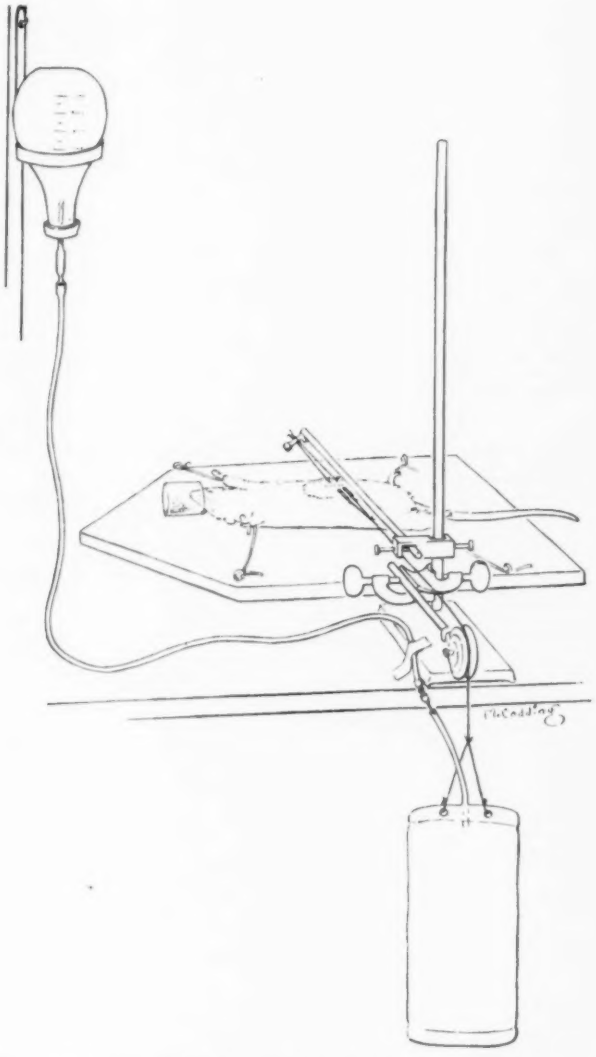

Fig. 1.—Apparatus for determining tensile strength of wounds in vivo. One wound edge is held stationary while increasing tension is applied to opposite edge by infusion of water into plastic bag.

RESULTS

Untreated Wounds.—A total of fifty primary wounds were tested on the third postoperative day. The tensile strength ranged from 0 to 253 grams, with a mean strength of 124 grams. The standard deviation of the group was computed from the formula $S = \frac{\sqrt{\Sigma(x - \bar{x})^2}}{n - 1}$ where x represents each individual observation, $\bar{x}$ indicates the mean, and n equals the number of observations. This was found to be ±60.

The wounds in seventeen of the fifty animals so tested were resutured and tested again three days later. The mean of the group was 569 grams with no value less than 336 grams, ranging as high as 830 grams. The standard deviation was ±140. No resutured wound was weaker than it had been as a three-day primary wound, and indeed all were at least three times as strong as on first testing (Table I).

TABLE I

RAT NO.	DAY 3 TENSILE STRENGTH (GRAMS)	DAY 6 TENSILE STRENGTH (GRAMS)
1	140	500
2	170	732
3	173	573
4	106	503
5	98	353
6	115	504
7	80	560
8	0	710
9	79	430
10	149	630
11	148	830
12	189	720
13	114	690
14	215	700
15	123	470
16	93	336
17	53	440

Comparison of these resutured wounds with a primary six-day wound was carried out. Twenty primary wounds were tested on the sixth day with a mean result of 817 grams, ranging from 450 to 1,150 grams.

Microscopic sections of the wounds were stained with hematoxylin and eosin. A primary three-day wound is filled with fibrin clot, with only slight evidence of fibroplastic activity (Fig. 2). In the resutured wound there is complete bridging of the incisional gap by proliferating fibroblasts (Fig. 3). The histologic appearance is the same as that of a primary wound six days old, except that the latter is somewhat better organized with less tissue edema.

Simulated Wounds.—While it seems obvious that local stimuli are responsible for the rapid rehealing of the resutured wound, the possible role of systemic factors derived from the metabolic changes occurring during the pituitary-adrenal stress response requires appraisal.

To accomplish this, two groups of animals, each consisting of eight rats, were given ACTH or cortisone in lieu of a primary wound. In one group each rat received Acthar Gel (Armour) 6 units intramuscularly daily for two days, and in the other group each rat received cortisone (Merck) 5 mg. intramuscularly daily for three days. These dosages were felt to be more than adequate to elicit a major metabolic response, thereby simulating the systemic reaction to wounding. Three days after the first dose of each drug had been given (at the same time as the first tensile strength was determined in the untreated ani-

mals), a standard test wound was made in both groups. The mean tensile strength on the third postoperative day was 126 grams in the cortisone group and 175 grams in the Acthar Gel group (Table II).

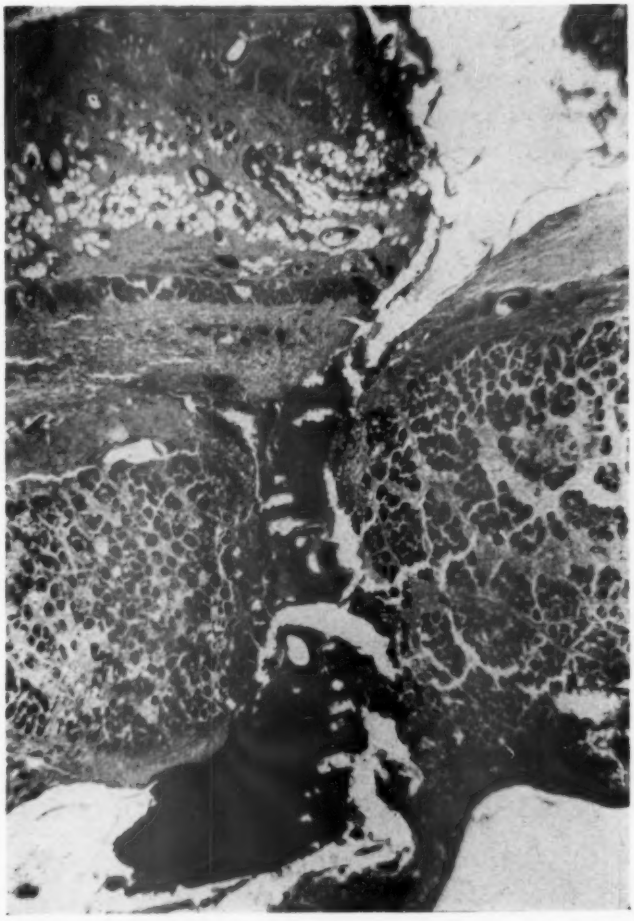

Fig. 2.—Photomicrograph of a normal three-day wound. Fibrin clot fills the incisional gap. (Hematoxylin-eosin stain; ×25, reduced ⅓.)

Local Excision of Wound Margins.—The importance of local factors in producing the increased rehealing phenomenon was evaluated by excising the wound margins after the first determination of tensile strength and then resuturing the wound. In five animals a 2 mm. margin of wound edge was excised. Three days later the mean tensile strength was 405 grams. Eight more animals were then treated similarly except that a 5 mm. margin of wound edge was excised on the third postoperative day. The mean tensile strength before excision was 138 grams. Three days later the mean tensile strength was 235 grams (Table III). As can be seen from Table III, two of the six-day values were slightly less than the corresponding three-day values. The effect of local excision in depressing but not completely abolishing the rehealing phenomenon suggests that local humoral factors may be at least partially responsible for the phenomenon.

Effect of Cortisone on the Healing of the Resutured Wound.—According to a recent report by Chassin,[6] severe preoperative stress or continuous treatment with cortisone beginning before operation lowers the strength of wounds tested on the fifth postoperative day. The effect of cortisone on the rehealing phenomenon was studied as follows:

Eleven rats were given 5 mg. of cortisone intramuscularly daily beginning two days before wounding and continuing thereafter for six days. Determinations of tensile strength were made on the third day, and the wound was then

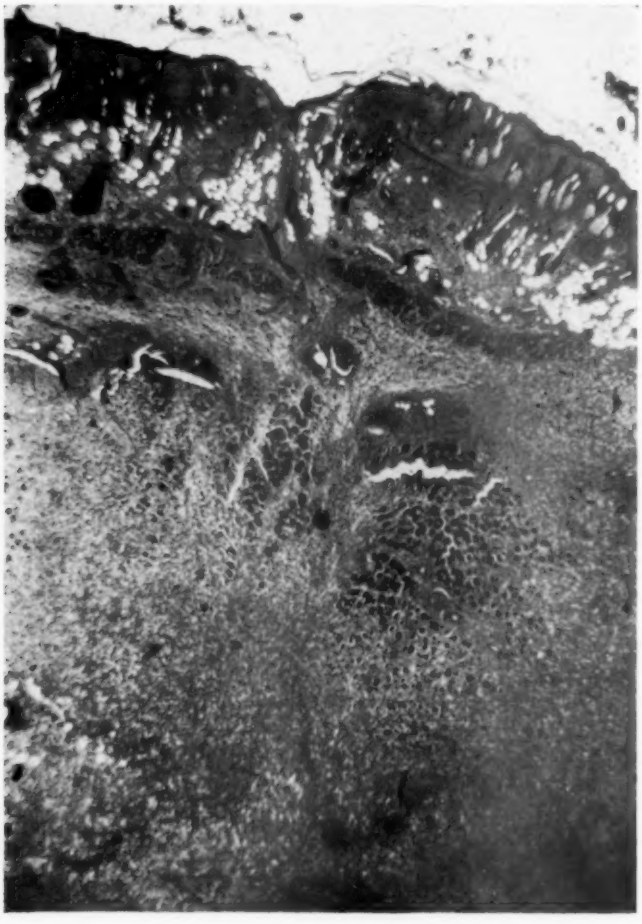

Fig. 3.—Photomicrograph of a wound which was disrupted on third day, then resutured. The incision has been bridged by fibroblasts and the clot has been completely replaced or removed. (Hematoxylin-eosin stain; ×25, reduced ⅕.)

resutured. The strength of the resutured wound was determined three days later. Of these, five animals had died by the sixth day and the rest had lost weight. The mean tensile strength of the primary three-day wound was 119 grams, approximately the same as in untreated rats. The mean tensile strength of the resutured wounds in the six survivors was only 121 grams, considerably less than a normal three-day resutured wound.

A second group of nine rats was treated similarly except that the cortisone was not started until the time of the first tensile strength determination, which averaged 136 grams. Three days later the mean tensile strength of the resutured wound was 520 grams. No animals died.

TABLE II

DAY 0	DAY 3 TENSILE STRENGTH (GRAMS)	DAY 6 TENSILE STRENGTH (GRAMS)
Wound	140	569
Dummy wound		
ACTH for 2 days	Wound	175
Cortisone for 3 days	Wound	126

The systemic response elicited by cortisone or ACTH does not stimulate the rehealing effect.

TABLE III

RAT NO.	DAY 0	DAY 3 TENSILE STRENGTH (GRAMS)	DAY 3 TREATMENT	DAY 6 TENSILE STRENGTH (GRAMS)
1	Wound made	43	Wounds excised and edges resutured	173
2	Wound made	243	Wounds excised and edges resutured	299
3	Wound made	176	Wounds excised and edges resutured	243
4	Wound made	23	Wounds excised and edges resutured	273
5	Wound made	95	Wounds excised and edges resutured	187
6	Wound made	195	Wounds excised and edges resutured	231
7	Wound made	253	Wounds excised and edges resutured	243
8	Wound made	73	Wounds excised and edges resutured	303
	Mean	183		235

Local excision of 5 mm. margin of wound edge on third day alters but does not eliminate the accelerated healing of the resutured wound.

These results, summarized in Table IV, indicate that if cortisone is given before initial wounding, it inhibits fibroplasia and abolishes healing not only in the primary wound but also in the resutured wound. However, if cortisone is given after the healing mechanism has been initiated, it does not prevent the accelerated healing of the resutured wound. Once cellular proliferation has begun, cortisone has little or no effect.

TABLE IV

	DAY 3 MEAN TENSILE STRENGTH (GRAMS)	DAY 6 MEAN TENSILE STRENGTH (GRAMS)
A	119	121
B	136	520

Effect of cortisone on rehealing phenomenon:

A, Cortisone 5 mg. daily started two days before wounding.

B, Cortisone 5 mg. daily started on day of first tensile strength determination.

Cortisone does not abolish the accelerated healing of the resutured wound unless it is given before the initial wound is made.

Effect of the Age of the Primary Wound.—In order to ascertain at what age a primary wound, when opened and resutured, will lose the ability to reheal with increased speed, a series of animals were wounded and allowed to heal for varying amounts of time up to forty days before the wound was in-

cised. All these wounds were then tested three days later. The results, summarized in Table V, indicate that the rehealing effect is at its height on the third day. This finding is not considered surprising since it has been shown that the growth potential of new fibroblasts equals that of a sarcoma or embryonic tissue.[7] As in Schilling's study of fibroblasts in tissue culture, the growth potential wanes over a six-week period.

TABLE V

AGE OF PRIMARY WOUND BEFORE DISRUPTION (DAYS)	NUMBER OF RATS TESTED	MEAN TENSILE STRENGTH AND STANDARD DEVIATION 3 DAYS AFTER DISRUPTION AND RESUTURE (GRAMS)
2	10	432 ± 91
3	17	569 ± 140
7	10	523 ± 126
15	15	378 ± 70
22	9	312 ± 70
28	5	302 ± 61
40	11	209 ± 79

The rehealing phenomenon is at its height in the first week after primary wounding, although the fifteen-day-old wound still exhibits a significant response and some effect appears to be present after forty days.

DISCUSSION

The most obvious and simplest explanation for the rapid assumption of strength by the resutured wound is that the process of cellular proliferation, interrupted temporarily by the disruption, is able to resume immediately without the usual latent period characteristic of the primary wound. Against this interpretation are (1) the failure of local excision of the wound before resuture to abolish the effect completely, and (2) the ability of the older wound (fifteen days or more) in which fibroplasia presumably is complete, to gain strength faster than a primary wound.

Systemic factors which might promote increased healing do not seem to be implicated. As mentioned earlier, we have shown that a preliminary wound elsewhere on the body does not elicit this effect, nor does the systemic response produced by stress, as simulated by cortisone or ACTH administration. On the contrary, these hormones, under certain conditions, may be detrimental to wound healing.

It is in the local environment of the healing wound that the factor or factors responsible for this phenomenon must be sought. Speculation concerning the cause is unprofitable at this time, but several hypotheses present themselves. In the past, a variety of wound hormones has been postulated. More recently, physical and chemical changes in healing tissue have been described, any one of which may be the fundamental process which promotes and ultimately limits fibroplasia. Elucidation of these factors is a challenge for continued study.

SUMMARY

It has been shown in the rat that a disrupted and resutured wound will acquire more strength by the third day than a primary three-day-old wound.

This phenomenon is particularly marked when a fresh wound less than one week old is disrupted, but can be observed to continue in decreasing degree for about forty days.

The rehealing phenomenon is not stimulated by the systemic effects of wounding or by corticoid administration.

Cortisone in large doses started before wounding retards healing and abolishes this effect in the three-day resutured wound. However, if started at the time of disruption of the primary wound, cortisone does not inhibit the accelerated healing of the resutured wound.

Wide excision of the wound edges at time of disruption greatly alters but does not eliminate the phenomenon.

The healing of the disrupted and resutured wound follows an accelerated pattern. The onset of fibroplasia seems to be earlier without the usual latent period. Local factors, the nature of which remains to be determined, are responsible for this.

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DISCUSSION

DR. DUNPHY.—I would just like to say that I do not know of anything that is more fascinating than the study of wound healing or anything that is more tedious to try to carry out in the laboratory, and I would like to congratulate Dr. Savlov on the amount of effort and time that he has put in, in trying to elucidate a few relatively simple facts and observations. This is a continuation of a study that I started back in 1938. I never published any of the data at that time because I was not convinced that the resutured wound does heal more rapidly than a primary wound. I am not certain that we should extend any of these observations to man, and I am also not certain that we have yet shown that the total curve of healing in a resutured wound is faster than in a primary wound. The resutured wound has a much faster take-off, and we have some observations which suggest to us that this is continued until healing is completed, but that is a matter which requires more study. It is possible that despite the faster take-off, the ultimate time when the resutured wound reaches maximum strength is not greatly different from that of a primary wound.

DR. FRANCIS MOORE (Boston, Mass.).—I would also like to congratulate Dr. Savlov and Dr. Dunphy on this work. I was hoping that this would stimulate a lot of discussion from the group about wound healing, but I think everybody is in the post-absorptive state or something and does not want to get up and make statements. I think

one of the major problems that confronts understanding of surgical patients today is the relationship of the systemic changes, about which so much work is going on, to the local changes in the wound, and one would assume that there must be some relationship, although the demonstration is yet to be made.

I have always felt from a clinical point of view that it is hard to imagine wound healing going any faster than Nature ordinarily makes it go. I have thought there was an analogy there with the rate of protein synthesis, which seems to me is a function of the total size of the lean tissue mass. It proceeds at a certain rate which is a result of temperature and enzyme activity, and you cannot speed it up. Yet Dr. Savlov has shown that this second wound at least starts much faster. I think the last slide, which he had to go through so quickly, showing that a local excision does not completely inhibit this, makes one feel that it is not just the fact that fibroblasts have met across the margin and have come together again but that there is in addition some other local factor involved. The cortisone data show that pretreatment with cortisone does inhibit the phenomenon but that if one starts the cortisone at the time of wounding, then he does not change what Nature has already begun. The significance in relation to endogenous hydrocortisone and wound healing is obvious.

DR. CLARENCE DENNIS (Brooklyn, N. Y.).—I feel that the paper presented by Dr. Savlov and Dr. Dunphy represents a very real contribution to our understanding of the nature of wound healing. Although the studies which Dr. Savlov described are all comparative studies, that is, comparing the strength of one wound in the healing phase with the strength of another wound at a different portion of the healing phase. I heard no reference with regard either to the absolute tensile strength of the healing wound or to the ratio which the wound held in various stages of the healing period to the intact abdominal wall prior to initial incision. Some studies which were made by Dr. John Fast in the Experimental Laboratory at the University of Minnesota indicated that the abdominal wound in the rabbit regains strength no greater than 83 per cent of the tensile strength of that abdominal wall prior to the time of incision. I should like, therefore, to ask whether Dr. Savlov and Dr. Dunphy made any determinations with regard to what part evisceration and resuture might play on the ratio of ultimate tensile strength to the original tensile strength of the abdominal wall.

DR. SAVLOV (Closing).—In answer to Dr. Dennis' question concerning studies on the ultimate strength of the wound, such studies are in progress and we hope to be able to report on them sometime in the future.

A STUDY OF CONSECUTIVELY HOMOGRAFTED SKIN ON C.F.W. MICE

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WE HAVE recently reported that splenectomy prolongs the survival rate of homologous skin grafts on C.F.W. mice[1] and that whole body irradiation produced permanent survival of homografts as determined by one year's observation period.[2] It was postulated that these procedures altered the immune mechanism, thus allowing the homografts to survive.

Medawar[3, 4] has demonstrated that a second homograft from the same donor to the same recipient would disintegrate at a faster rate than the first. These observations were explained by a mechanism conforming to the theories of an immune reaction. Both Dempster[5] and Medawar[3, 4] have stressed the importance of skin dosage and have shown that the greater the dosage, the faster the disintegration of the transplants.

The present study was formulated to test the hypothesis that the application of homologous, consecutive, and randomly selected homografts would alter the immune mechanism of the recipient and thereby affect the survival of the graft.

METHODS

A study of 201 homologous skin grafts was made, obtaining the transplants from 6-week-old heterozygous C.F.W. mice. The average weight of the animals was about 20 grams. Anesthesia consisted of 0.5 to 0.8 c.c. of a 5 per cent solution of Nembutal sodium injected intraperitoneally. Ninety-four consecutive grafts were placed on mice which were splenectomized one week previous to the initial homograft. A total of three consecutive grafts were made in this series. The time interval between each homograft varied from thirty to forty-nine days. The consecutive homografts were secured in all instances from heterozygous donors. The skin transplants were free full-thickness grafts, weighing 150 mg., and had an area of 1 sq. cm. The graft, when procured, was cut sharply away from the underlying subcutaneous tissue. Fixation of the homografts to a corresponding defect on the recipient animal was accomplished by means of interrupted and continuous 0000 black silk suture. The entire graft was covered with a thin layer of collodion. In another series, 107 homografts were applied to nonsplenectomized mice. In this group of animals the time intervals between homografts varied from thirty to ninety days. Three or four grafts were consecutively applied to each recipient.

A consecutive, additional homograft was not applied until the previous homograft had been completely rejected. The criteria for the determination of recording the permanency of a graft is as stated in a previous paper.[1]

The grafted mice were placed in individual cages and observed daily. The minimal observation period to date is 120 days. A portion of the surviving homografts have been observed for ten months.

RESULTS

Survival Rate of Consecutive Homografts on Nonsplenectomized C.F.W. Mice.—(See Table I.) Forty mice receiving an initial homograft had completely rejected the transplants by ten days.

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Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

TABLE I. EFFECT OF CONSECUTIVE HOMOGRAFTING ON THE SURVIVAL OF C.F.W. MOUSE SKIN ON NONSPLENECTOMIZED RECIPIENTS*

NO. OF SKIN GRAFT	NO. OF MICE	NO. OF DAYS BETWEEN TRANSPLANTATIONS	NO. OF VIABLE GRAFTS†
1	20	0	0/20
2	14	30	0/14
3	14	30	0/14
4	14	30	5/14
1	20	0	0/20
2	16	60	6/16
3	9	90	4/ 9

*Minimum observation period of 120 days.
†Viable grafts/total number.

Similarly, a second series of fourteen homografts applied thirty days after the initial transplant were also rejected by each recipient. However, when a sixty-day interval elapsed between the initial and second homograft in sixteen mice, six of these transplants remained viable after nine months.

A third skin graft applied to fourteen mice, thirty days after the second transplant, resulted in no viable grafts. When ninety days was allowed to elapse after the second transplant, four of the nine grafts were alive after six months.

A fourth homograft applied thirty days after the third transplant in fourteen animals resulted in five viable grafts. These grafts still showed all the characteristics of permanency at ten months. All the permanent grafts mentioned in this paper are being preserved for a follow-up period for the natural life span of the animal.

Survival Rate of Consecutive Homografts on Splenectomized C.F.W. Mice.—(See Table II.) Thirty-seven mice were grafted with an initial homologous transplant. Nineteen days later all these grafts had become necrotic.

TABLE II. EFFECT OF CONSECUTIVE HOMOGRAFTING ON THE SURVIVAL OF C.F.W. MOUSE SKIN ON SPLENECTOMIZED RECIPIENTS*

NO. OF SKIN GRAFT	NO. OF MICE	NO. OF DAYS BETWEEN TRANSPLANTATIONS	NO. OF VIABLE GRAFTS†
1	17	0	0/17
2	17	30	1/17
3	16	36	4/16
1	20	0	0/20
2	18	49	7/18
3	6	30	3/6

*Minimum observation period of 120 days.
†Viable grafts/total number.

A second graft was applied to each of thirty-five mice either thirty or forty-nine days after the first transplant. In the thirty-day series, only one graft survived and has been observed eleven months. In the forty-nine-day series, seven grafts survived and have been under observation for ten months.

Twenty-two animals received a third transplant thirty or thirty-six days after the second graft. This resulted in three viable grafts in the thirty-day group and four in the thirty-six-day group. These grafts were observed for five and ten months, respectively.

DISCUSSION

Consecutively homografted skin obtained from different donors resulted in a permanent survival for thirty of 201 grafts. The time interval between successive transplants was an important contributory factor influencing the survival of the homografts.

When this time interval between the first and second grafts was thirty days, both sets of homografts were rejected by the tenth day. When a third series of homografts was applied after the same thirty-day time interval, all the grafts did not become completely necrotic before twenty-four days. It was not until the fourth transplant was applied, thirty days after the preceding graft, that permanent viability was observed.

In contrast to these findings, when sixty or ninety days intervened between consecutive grafts, permanent viability occurred in both the second and third series of homografts.

It seems that these observations could be explained by the concept of "immunoparalysis," as described by Felton[6] and Morgan and associates.[7]

Our observations on the fate of consecutively applied homografts depend on at least two variables: time of application and dosage of skin. Thus the transplantation of consecutive skin grafts, at thirty-day intervals is postulated to hold the immune mechanism in abeyance. Temporary or permanent viability of the homografts was also dependent upon the number of grafts applied.

When the time interval between grafts was extended to sixty and ninety days, fewer consecutive grafts, representing a smaller dosage of skin, were necessary in order to obtain permanent viability. It should be kept in mind that in another immunologic phenomenon, that of anaphylaxis, time and antigen dosage are also of great importance.

Splenectomy performed prior to consecutive skin grafting again substantiated our earlier observation that immune mechanism may have been depressed, probably on a quantitative basis.[1] This was well shown by a permanent survival of the second as well as the third grafts when the time interval was approximately thirty days.

CONCLUSION

Permanent survival of homologous skin grafts on heterozygous C.F.W. mice has been produced by subjecting the recipients to consecutive skin grafts from dissimilar donors. The observation period at the time of this report has been ten months. The factors influencing these results include dosage of skin, time intervals between grafts, and the quantitative depression of the reticuloendothelial system by splenectomy.

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DISCUSSION

DR. EDWARD L. HOWES (New York, N. Y.).—May I ask what the lymphatic count was in those animals that were heavily x-rayed. I would like to report that Medawar succeeded with homologous transplantation by putting the recipient's white blood cells into the donor during embryonal life. He has not reported this yet.

DR. HERBERT CONWAY (New York, N. Y.).—I think that this work of Dr. Hardin and Dr. Werder is very creditable. I have had the pleasure of visiting their laboratory and can attest to the fact that they not only run large numbers of animal experiments, but that their work is very careful and well controlled.

There is, however, discrepancy between their findings and those in our laboratory at Cornell in that we have not been able to make skin grafting permanently successful (homologously) from one strain of mice to another. In that respect we vary with Medawar, too, whose name is so well known in the field of immunology. The reason for the use of mice as experimental animals is that their life span is very short, two years. A mouse can be carried through many generations in a relatively brief period of time.

In this country, through the benefit of the Jackson Memorial Laboratory at Bar Harbor, we can obtain many diverse strains of mice, so I presume that genetic differences account for whether one laboratory gets permanent takes and another one does not. In our experiments we have insisted on the use of widely divergent strains of mice.

The three theories as to the cause of failure of compatibility of a graft between given individuals of the same species relate to: first, blood incompatibility; second, the so-called geneticocellular or organismal differential theory; third, the immune concept which has been advanced by Medawar. The strength of the argument for the immune theory rests on the fact that the second set of grafts sloughs faster than the first set of grafts, both sets being taken from the same donor.

Dr. Hardin's experiments have been directed toward an attempt to fatigue the immune mechanism. I think this is a very sound approach to the problem.

The single defect in the immune theory as a cause of failure in homoplastic skin grafting is that no one has yet identified the immune body, no one has isolated it, no one has been able to find it. Therefore, the concept of immune reaction as a cause of failure of homoplastic skin grafts is still a theory.

DR. HARDIN (Closing).—In answer to the query on the lymphatic count, there is so much diverse reporting in the literature; we have been trying to do it but we have been very unsuccessful. There is a great deal of variance in how you take the count, whether you bleed the animal from the tail or from other areas of the body, that the results, we feel, are not very accurate.

In reply to Dr. Conway, we, too, have realized that the basis of this work depends upon the total dissimilarity of the animals that are used as donors, and because of that, we have been running a large series of animals. I think we have now in our series grafted over 4,000 mice, and in this last presentation of multiple grafts, we had to make 200 transplants before we got thirty takes. So again it shows the importance of using large numbers of animals.

Everyone today has commented on the immune theory and, of course, it is an alluring one. We are making electrophoretic studies on the gamma globulin fraction and think that perhaps there is some change here. The immune response is perhaps a mechanism so obscure that we should not think about it in the conventional manner as evoking a circulating antibody. It may be local, and further work will have to be done on that score.

A STUDY OF LIVER DAMAGE FOLLOWING INDUCED HYPOTENSION

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WITH the advent of hypotensive anesthesia using ganglionic-blocking drugs, it appeared necessary to evaluate the effect of these techniques on such organs as the liver, brain, kidney, and heart. As yet, relatively little is known of the permanent or temporary disability experienced by these vital organs as a result of reducing drastically the peripheral arteriolar resistance for varying lengths of time. Morris and associates[1] have reported recently a study of the vascular dynamics in the brain and kidney during controlled hypotension using hexamethonium drugs. They concluded that there was little danger of cerebral or renal anoxia in the supine patient with a mean blood pressure of as low as 55 mm. Hg using hexamethonium-induced controlled hypotension. Bromage[2] has described gross changes in the liver during seventeen laparotomies under high epidural spinal anesthesia; no microscopic or chemical studies were recorded. He stated that the vascular hypotension induced by sympathetic block might produce local hypoxia in the liver before other tissues were affected. At systolic pressures between 45 and 60 mm. Hg, fourteen of seventeen livers appeared cyanosed, and eleven became turgid and rubbery. These changes were reversed when the blood pressure was raised by Methedrine or noradrenaline.

The purpose of this study was to evaluate the extent of liver damage incurred following hypotension produced by abolishing the peripheral arteriolar resistance for varying lengths of time. We have been unable to find any specific study of the late sequelae of hemorrhagic shock at 30 mm. Hg for thirty or forty-five minutes. However, since the acute effects of hemorrhagic hypotension on the liver have been studied so extensively by Blalock,[3] Frank, Seligman, and Fine,[4] Delorme,[5] Wilhelmi, Russell, Engel, and Long,[6] and numerous others,[7-14] it was used in a parallel study for comparison with the effect of induced chemical hypotension. Friedman, Frank, and Fine[13] have shown that in hemorrhagic hypotension there is constriction of the intrahepatic veins which accounts for the increase in hepatic vascular resistance. Chute[14] has summarized the recent knowledge of the changes in liver function during hemorrhagic shock. He stated that all the changes appeared to spring from a reduced oxygen supply and especially from a lowered oxygen tension within the liver; he also reported that galactose and Bromsulfphalein excretion were also reduced.

METHODS AND MATERIALS

The following biochemical determinations were effected in each of forty-one dogs prior to and biweekly following a controlled period of hypotension: blood nonprotein nitrogen,

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serum chlorides, sodium, potassium, carbon dioxide-combining power, Bromsulfphalein retention, thymol turbidity and flocculation, and serum bilirubin. After obtaining these biochemical studies for a base line, the dogs were anesthetized with intravenous pentobarbital sodium and maintained on 100 per cent oxygen via an endotracheal tube connected to a nonrebreathing valve. Respirations were controlled or assisted when necessary to insure adequate oxygenation. A large polyethylene catheter was introduced into the inferior vena cava via the femoral vein, and a cannula was inserted into the femoral artery and connected to a constant blood pressure-recording kymograph. Twenty-one dogs received an intravenous drip of d-3, 4 (1^1, 3^1-dibenzyl-2^1-ketoimidazolids)-1, 2 trimethylene thiophanium d-camphor sulfonate (Arfonad*),[15] a ganglionic-blocking drug; the blood pressure dropped rapidly to a mean pressure of 30 mm. Hg, where it was maintained for the desired length of time. The hypotensive state was maintained for thirty minutes in ten dogs and forty-five minutes in eleven dogs. The level of 30 to 32 mm. Hg was selected since, according to Landis,[16] that is the approximate level at which the peripheral arteriolar resistance is abolished; this leaves 30 to 32 mm. Hg to overcome the pressure in the venous system and the osmotic pressure of the plasma proteins. At the end of the hypotensive period, the drug was discontinued, and the pressure rose gradually to normal. Vasopressor drugs, namely, Vasoxyl and Levophed, were given by continuous intravenous drip to aid in restoring the blood pressure to normal levels in some dogs.

For comparison, twenty other dogs were rendered hypotensive by rapid bleeding via the large catheter in the vena cava until a mean pressure of 30 mm. Hg was obtained. By the intermittent withdrawal of small increments of blood, this mean pressure of 30 to 32 mm. Hg was maintained for thirty minutes in ten dogs and for forty-five minutes in the other ten dogs. At the end of the desired period of hypotension, the blood withdrawn was returned. The survivors of the experiment were sacrificed after a fifteen- to thirty-day period by an overdose of intravenous Nembutal, and autopsy studies of the thoracic and abdominal viscera were carried out immediately thereafter with special emphasis on the histologic changes in the liver parenchyma. Every dog received aqueous penicillin, 10,000 units, and procaine penicillin, 300,000 units, at the beginning of the hypotensive state and procaine penicillin, 300,000 units, each day during the first week of survival.

RESULTS

The mortality rate in the hemorrhagic group was higher than in the chemical hypotensive group. Prolongation of the hypotensive state further increased the mortality rate in both groups.

TABLE I. MORTALITY RATE

TYPE OF HYPOTENSION	DURATION (MIN.)	NO. OF DOGS	PER CENT
Chemical	30	1/10	10
Chemical	45	4/11	36
Hemorrhagic	30	4/10	40
Hemorrhagic	45	6/10	60

Positive biochemical evidence of liver damage in the survivors was judged to be present when the Bromsulfphalein retention was over 5 per cent in thirty minutes, the thymol turbidity was over 3 units, or the thymol flocculation over 1 plus.

In the survivors of each group there was relatively little difference in the biochemical evidence of liver damage. All the abnormal tests except one were transient appearing between the third and twenty-first days following the hypotensive period.

*Supplied by Hoffmann-La Roche, Inc., Nutley, New Jersey.

In the chemical hypotension group, one of the nine surviving dogs in the thirty-minute group had a Bromsulfphalein retention of 10 per cent on the third day. In the forty-five-minute group, three of the seven surviving dogs had abnormal tests; two had Bromsulfphalein retentions of 15 per cent and 20 per cent on the third and fifteenth day, respectively; one dog had a thymol flocculation of 2 plus on the fifteenth day. Likewise, in the hemorrhagic hypotension group, only one of the six surviving dogs in the thirty-minute group had a Bromsulfphalein retention of 25 per cent on the eighth day. Furthermore, in the forty-five-minute group, only one of four surviving dogs had an abnormal test, with a thymol turbidity of 7.5 units noted for the first time on the twenty-first day and persisting to the time of autopsy on the twenty-sixth day (see Table II).

TABLE II. RESULT OF BIOCHEMICAL STUDIES IN THE VARIOUS GROUPS

30-MINUTE GROUP	45-MINUTE GROUP
Chemical Hypotension	
Dog # 4 BSP retention 10% on third day	Dog # 8 Died, "irreversible"
Dog # 5 Negative	Dog # 9 Died third day
Dog # 6 Negative	Dog #11 Died first day
Dog # 7 Negative	Dog #13 Negative
Dog #20 Negative	Dog #14 BSP retention 15% on third day
Dog #21 Negative	Dog #15 Negative
Dog #36 Negative	Dog #17 Negative
Dog #37 Negative	Dog #18 BSP retention 20% on fifteenth day
Dog #38 Died first day	Dog #19 Thymol flocculation 2 plus on fifteenth day
Dog #39 Negative	Dog #22 Died tenth day
	Dog #36 Negative
Hemorrhagic Hypotension	
Dog #82 BSP retention 25% on eighth day	Dog #27 Negative
Dog #85 Negative	Dog #28 Died third day
Dog # 1 Negative	Dog #29 Negative
Dog #23 Died first day	Dog #30 Died second day
Dog #24 Negative	Dog #31 Died, "irreversible"
Dog #25 Died, "irreversible"	Dog #32 Thymol turbidity 7.5 units on twenty-first day
Dog #35 Negative	Dog #33 Died first day
Dog #40 Died second day	Dog #43 Died first day
Dog #41 Died first day	Dog #44 Died second day
Dog #42 Negative	Dog #34 Negative

There was no appreciable change in the blood nonprotein nitrogen or serum electrolytes of any of the dogs.

With regard to the time of death, the only fatality in the thirty-minute chemical group occurred on the first postoperative day, when the dog was found dead in its cage. In the forty-five-minute chemical group, one dog went into so-called "irreversible shock"; a second dog died on the first postoperative day, a third on the third day, and a fourth on the tenth day.

In the thirty-minute hemorrhagic group, one dog developed "irreversible shock" and died at the conclusion of the experiment; two died on the first postoperative day and one on the second postoperative day.

In the forty-five-minute hemorrhagic group, one developed irreversible shock; three died on the third postoperative day and two on the second postoperative day (see Table II).

HISTOPATHOLOGIC STUDIES

The tissues were placed in 10 per cent formalin and later refixed in Vande-Grift's fixative. Sections were stained with hematoxylin and eosin and, whenever necessary for further study, by periodic acid stain, Masson trichrome stain, and Wilder reticulum stain. Sudan IV was used in staining fats.

In studying the liver sections, the following conditions were searched for and graded on a comparative basis using a one to four scale: eosinophilic granularity of the cytoplasm, nonlipid, nonglycogenic vacuoles, fat vacuoles, necrosis, pyknosis of nuclei, multiple nuclei, variation in nuclear size, mitoses, presence or absence of bile pigment in liver cells or in macrophages in portal areas, relative size of the liver cells, dilatation of central veins or sinuses, inflammatory reaction, and fibrosis. Special notation was made of the area of the liver lobule, that is, the paracentral, mid-zonal, or portal portion, which was most affected. These observations were correlated with one another, and then the individual livers as units were comparatively graded from one to four.

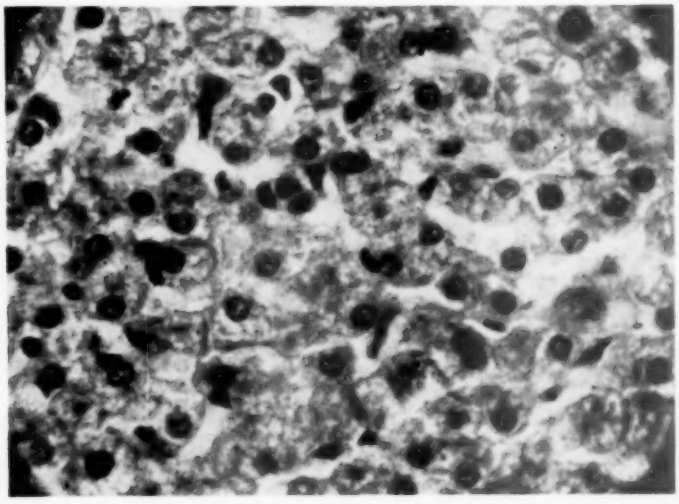

Fig. 1.—Dog No. 5. Normal-appearing liver. Dog was sacrificed seventeen days after a thirty-minute period of chemical hypotension. Occasional double nuclei are evident. Liver function tests were normal.

Evidence of significant cellular damage such as eosinophilic granularity of the cytoplasm, pyknosis of nuclei, and dissolution of cells was present only in those animals dying in the immediate postoperative period and in Dog No. 85. In the two dogs dying within twenty-four hours, the paracentral sinuses and veins were dilated and engorged with blood; in some areas, actual hemorrhage was suggested. The paracentral cells showed early changes of necrosis. In the dogs dying in twenty-four to twenty-eight hours, fine droplets of sudanophilic material appeared in addition to an increase in the other evidences of cellular damage and necrosis. The kidneys of animals dying within the two postoperative days showed cloudy swelling of the tubular epithelium. The other organs examined showed no remarkable changes.

Fat vacuoles occurred in only one animal living beyond the immediate postoperative period. This animal (No. 35) had been subjected to thirty minutes of hemorrhagic shock. The vacuoles were large, few in number, and showed no

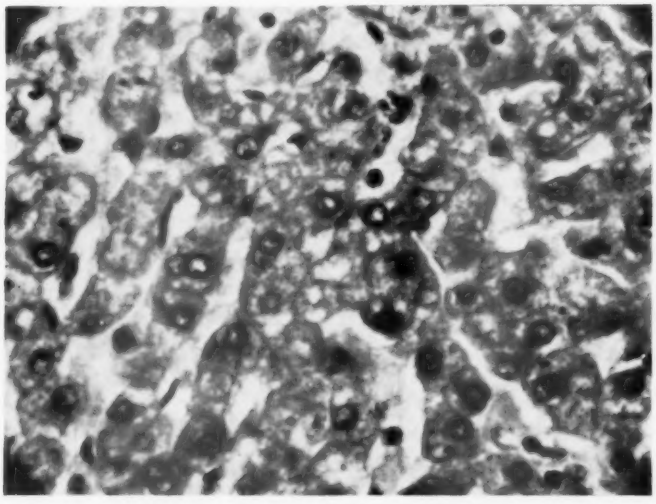

Fig. 2.—Dog No. 6. Dilated sinuses, nonlipid, nonglycogenic vacuoles and double nuclei are evident. Dog was sacrificed seventeen days after a thirty-minute period of chemical hypotension. Liver function tests were normal.

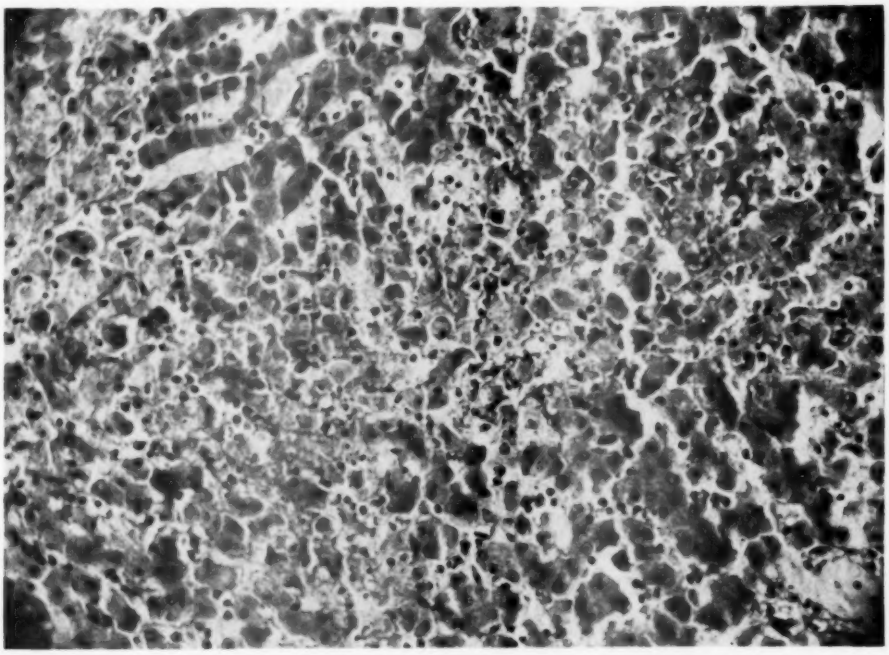

Fig. 3.—Dog No. 43. Central necrosis occurring in a dog that died on the first day following a forty-five-minute period of hemorrhagic hypotension.

tendency to be concentrated in any one portion of the lobules. Vacuoles such as these are occasionally present in the livers of mongrel dogs without experimental injury to the liver and on apparently adequate diets.

Double nuclei and nuclear variations in size were occasionally present in the more central portions of the lobules of many of the dogs. However, the number of cells containing such nuclei was approximately the same as that present in a series of mongrel dogs without dietary or experimental injury to the liver. These are generally accepted as indications of cellular regeneration and indicate that at this period no significant regeneration was occurring.[17, 18] Mitotic figures were not present in any of the material.

The liver of one dog (No. 85) contained one large abscess and numerous other small areas showing gradations from acute inflammatory reaction to small granulomata. Necrosis of parenchymal cells occurred in the areas of more acute reaction. These foci were present in all three portions of the liver lobules. No bacteria or fungi were stainable in these lesions. We interpret them to be of an infectious etiology and not related to the period of hypotension. We have occasionally seen such granulomata in the liver and kidneys of other dogs not subjected to experimental or renal damage. The sections of spleen, adrenals, heart, lungs, and kidneys of this animal showed no significant changes. Occasionally a few lymphocytes and plasma cells were present in the portal areas of the livers of other dogs. These were no more common or more severe than those present in a series of mongrel dogs without experimental liver injury.

The nonlipid, nonglycogenic vacuoles are considered to be of no importance as indicators of significant liver injury. They occurred in animals with moderate or low amounts of glycogen and varying degrees of congestion, as indicated by the periodic acid stains and dilatation of the sinuses, respectively. This is in agreement with the work of Trowell[19] and others.[20] They demonstrated that such vacuoles appeared in the livers of animals with normal or low levels of glycogen when the livers were subjected to anoxia or increased intrasinusoidal pressures or combinations of these two factors. The vacuoles appeared in some of Trowell's animals within thirty seconds after the production of circulatory obstruction or anoxia. They disappeared within thirty minutes after the anoxia or circulatory obstruction was relieved. Trowell also demonstrated that if the intrasinusoidal pressure is allowed to remain elevated in an animal killed by asphyxia or anoxia and the autopsy is delayed for five to fifteen minutes, such vacuoles will develop. We interpret them to be the results of the combination of the method of sacrifice, low glycogen content, and slight delay in completing the gross autopsy studies.

None of the other organs examined showed significant changes. These included the heart, lungs, kidneys, and adrenals.

In summary, the only signficant changes occurred in animals dying within two days following the period of hypotension. These consisted of necrosis of paracentral cells and dilatation of the paracentral sinuses in the first twenty-four hours. In the twenty-four- to forty-eight-hour period, necrosis of parenchymal cells became more obvious and more extensive. In addition, the paracentral cells contained numerous, small sudanophilic globules. The changes are of a nonspecific nature but are frequently attributed by Himsworth[18, 20] to the effects of anoxia.

COMMENT

In this experiment two fundamentally different syndromes are studied in which the common denominator is hypotension at a mean pressure of 30 mm. Hg for thirty and forty-five minutes.

In hemorrhagic hypotension, Friedman, Frank, and Fine[13] have shown that the portal veins constrict and sometimes do not recover their normal caliber for over six hours. Portal venous pressure measurements indicated an increase in intrahepatic vascular resistance during hemorrhagic hypotension, which persisted after transfusion. They concluded that the constriction of the intrahepatic veins accounted in large degree for the increase in hepatic vascular resistance.

In chemically induced hypotension, the blood volume is not decreased; hence, in the presence of adequate oxygenation, the drop in peripheral arteriolar resistance means better perfusion of tissues as opposed to the vasoconstriction in the hemorrhagic syndrome.

In a recent review Engel[7] stated that all metabolic changes described during shock can be attributed to the consequences of hypoxia affecting different organs and tissues of the body to varying degrees. He pointed out that during shock, the blood and oxygen supply of certain organs, such as the liver and kidneys, may become limited to a much greater degree than that of other organs, such as the heart and the brain; different organ systems had different sensitivities to comparable degrees of hypoxia. The adjustments which occurred appeared to be of such a nature as to preserve to the last the blood supply for the most sensitive and least expendable organs.

In this study, autopsy examination of the thoracoabdominal organs of the dogs dying within three days of the hypotensive period revealed marked liver damage. There was no difference in degree of liver damage between the chemical blockade or the hemorrhagic groups dying after the hypotensive period. Yet, the kidneys, lungs, adrenals, and heart appeared essentially unremarkable. It is, therefore, hypothesized that with the possible exception of the brain (which was not studied) the liver is the most sensitive organ to the degree of hypoxia produced under the conditions of this experiment. In the survivors of all groups, evidence of biochemical damage to the liver or kidney was scanty; the surviving dogs also failed to show any marked changes in the histologic sections of the liver and the other thoracic and abdominal vital organs.

The mortality rate was slightly higher in the dogs rendered hypotensive by hemorrhage, perhaps again because of the difference in the mechanism of the hypotension. The vasoconstriction accompanying hemorrhage would certainly be more detrimental than the drop in peripheral arteriolar resistance.

There was also a statistically significant difference in mortality and morbidity when the chemically induced hypotension was prolonged from thirty minutes to forty-five minutes. Again, this may be explained on the basis of prolongation of relative hypoxia.

As for the other vital organs, Morris and associates[1] have recently shown that the hexamethonium drugs produce a decrease in cerebral blood flow followed by marked depression in the mean blood pressure in spite of a decrease

in cerebral vascular resistance; cerebral oxygen consumption was only slightly decreased due to a more complete extraction of oxygen from the blood flowing through the brain. As for the kidney, their studies revealed that initially the glomerular filtration rate and renal plasma flow were both depressed. After two to three hours of maintained hypotension, renal plasma flow returned to control levels, whereas glomerular filtration rate remained depressed. The hexamethonium-induced hypotension decreased urine formation, and blood volume was slightly increased predominantly because of an increase in plasma volume. They concluded that there was little danger of cerebral or renal anoxia in the supine patient with a mean blood pressure of as low as 55 mm. Hg when hexamethonium-induced controlled hypotension was employed. There is no specific reference to the effect of length of the hypotensive state. Similar studies with comparable results have been reported by MacKinnon[21] and McQueen.[22] In our study a hypotensive state at 30 mm. Hg for as long as forty-five minutes by chemical blockade or hemorrhage did not reveal any discernible anatomic change in the kidney or elevation in the blood nonprotein nitrogen level.

The importance of having preserved adequate respiratory function during the experiments with the use of oxygen when indicated should be stressed. Every effort was made to prevent anoxic anoxia from being a complicating factor in this series.

The use of antibiotic drugs during and immediately following the hypotensive state has been demonstrated by Fine.[23] Chute,[14] in his review, stated that since penicillin prevents the death of a normal dog with a ligated hepatic artery, it would seem certain to be of benefit to the anoxic liver of individuals in shock. He emphasized that suitable antibiotics should rank with blood volume replacement in the therapy of shock. In order to obviate any complicating factor of infection in this study, all dogs received aqueous penicillin and procaine penicillin on the day of the experiment and during the first week of the survival period. There was no evidence of bacterial invasion in the histologic studies of the liver parenchyma in the sections from the surviving dogs or the dogs dying following the experiment.

Further studies to evaluate the changes in liver function and the portal venous system during chemically induced hypotension are to be carried out.

SUMMARY AND CONCLUSIONS

1. In dogs, the mortality rate following the production of a hypotensive state at a mean pressure of 30 mm. Hg for thirty to forty-five minutes is somewhat lower when the hypotension is produced by a chemical ganglionic-blocking drug than by hemorrhage.

2. There is a statistically significant difference in mortality and morbidity when the hypotensive state is prolonged from thirty to forty-five minutes by chemical blockade. The difference is not statistically significant in the hemorrhagic group.

3. In the dogs surviving the hypotensive state produced either by chemical blockade or hemorrhage, discernible liver damage by biochemical function tests

and histopathologic studies was minimal fifteen to thirty days following the period of hypotension.

4. In all dogs dying within three days following the period of hypotension, there was evidence of marked liver damage.

5. There were no significant alterations in the kidneys, adrenals, heart, or lungs of any of the dogs submitted to hypotension. In the surviving dogs there was no elevation of the blood nonprotein nitrogen or any alteration in serum electrolytes.

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EXPERIMENTAL STUDIES ON TEMPORARY OCCLUSION OF THE INFERIOR VENA CAVA

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MOST patients whose lives are threatened by a potential pulmonary embolus can be treated satisfactorily by anticoagulants or by superficial femoral vein ligations, or by a combination of the two. There remains a limited group of such patients, however, for whom ligation of the inferior vena cava is the procedure of choice.

Numerous reports[1-6] have dealt with the late effects of caval ligation. Unfortunately, the persistence, or the development, of undesirable sequelae after ligation of the inferior vena cava is not rare. The most pessimistic of the follow-up reports is that of Shea and Robertson,[7] who carefully studied a group of twenty-five patients who had had ligation of the inferior vena cava four or more years previously. Only sixteen patients in the group had returned to full normal activity, and the majority had had signs and symptoms of an impaired circulation of the lower extremities.

Persistent or recurrent venous pathology, frequently present along with the edema or ulceration, has been implicated rather than the caval ligation as the cause of the undesirable sequelae. It is suggested that caval occlusion may materially influence the recurrence of venous pathology. Increased venous pressure, commonly present after ligation of the vena cava, may lead to venous stasis and thus promote thrombosis in the veins of the lower extremities. In this manner, the caval occlusion may be responsible, although indirectly, for the unpleasant sequelae.

The possibility that a permanently occluded inferior vena cava may contribute, either directly or indirectly, to the discomfort of these patients has prompted us to seek a method of producing an occlusion of the vena cava which need not be permanent.

Streuter and Paine[8] demonstrated in a series of thirty-four dogs that the occlusion produced by a catgut ligature about the inferior vena cava was only temporary in 82 per cent. The average time following surgery at which reopening was demonstrated was six weeks, and this interval was not varied predictably by using different sizes of plain or chromic catgut. A distinct disadvantage of the method was the early opening of the vena cava in some instances. Patency, which was demonstrated in one animal on the eighteenth day, actually may have been present sooner in several dogs, and over one-third of the ligated vessels which reopened did so within thirty days.

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Our efforts were directed toward producing a temporary occlusion of the inferior vena cava which would permit a reopening of the vena cava after any chosen interval of time.

The characteristics of the venous pressures and collaterals during and after such occlusions were investigated.

METHODS

The vena cava in a series of forty mongrel dogs was occluded by either a tie or a clip. The ties were of umbilical tape in three dogs, No. 20 cotton in nineteen, collagen in one, and polyethylene tubing in one. The special stainless steel clip, used in sixteen animals, was so made that there was less than a 0.3 mm. gap between its two prongs after it was inserted into a polyethylene "button." The size and characteristics of the clips were changed slightly as work progressed (Fig. 1).

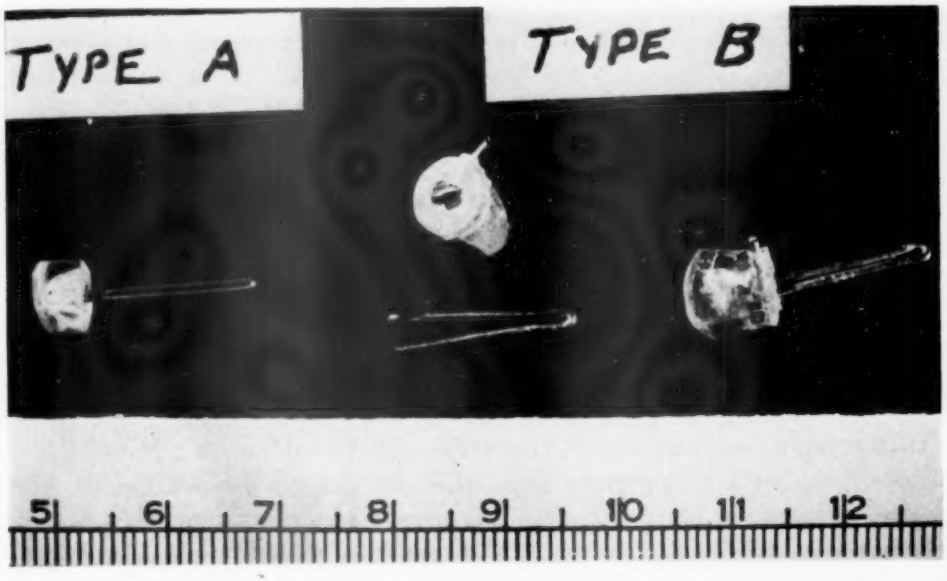


Fig. 1.—Stainless steel clips. *Type A*, used in early part of series, and *Type B*, used later, and preferred. The gap between the prongs can be predetermined with accuracy. The button contains a wire, visible roentgenographically, which fits into the grooves on the prongs and prevents the clip from slipping off the vena cava. The medially placed button becomes encased in fibrous tissue and remains stationary, allowing the clip to be removed by lateral traction.

Operations, venous pressure studies, and venograms were performed under intravenous Nembutal anesthesia. The inferior vena cava, exposed through a right paramedian incision, was occluded at about the level of the third lumbar vertebra. If a ligature was used, it was tied just tightly enough to occlude the lumen completely. When a clip was used, its prongs were spread and held open by a hemostat while being slipped over the vena cava toward the midline. The prongs were then held together as the button was slipped over the medial ends. The moderate spring of the metal was sufficient to maintain a constant relationship between the clip and its button. A silk suture, previously tied to the apex of the clip, was worked retroperitoneally to, and through, the right anterolateral abdominal wall, where it was fastened to a small, subcutaneously placed polyethylene button. This suture was kept loose at all times, with enough slack to prevent tension on the clip as the animal moved about postoperatively.

At the second operation, the vena cava was exposed similarly, in the attempt to preserve the venous collaterals. The tie about the vena cava was isolated, cut, and removed. When

a clip had been used, the vena cava was exposed similarly, with the subcutaneous button exposed through a separate incision. With the clip, its button, and the vena cava under direct vision, traction was applied to the pull-out suture subcutaneously, pulling the clip out of its button, away from the vena cava, and on out through the abdominal wall. The button lying medial to the vena cava was not disturbed. If the tie was broken, the clip was removed by direct traction to its lateral end.

Femoral venous pressures were observed continuously during and immediately after occlusion of the inferior vena cava in twenty-one dogs. If the needle in the vein became occluded, as happened not infrequently, a fresh needle was substituted. Follow-up femoral vein pressures were determined in twenty-three dogs from twenty-four hours to six months after caval occlusion.

Fifty-six venograms were made in twenty-four dogs through an exposed femoral vein. Twenty-five cubic centimeters of 70 per cent Diodrast* was injected rapidly, the exposure being made as the injection was nearing completion. When the injection was made directly into the femoral vein, only the collaterals on that side were well outlined. Better symmetrical filling was obtained by injecting through a large polyethylene catheter inserted, through the femoral vein, well into the common iliac vein. This latter method was used most often.

An autopsy was performed at the time of sacrifice or soon after death in thirty-one instances, particular attention being paid to the site of occlusion. In some, the lungs were examined grossly for the possibility of infarcts. Microscopic slides and photographs were made of representative occlusion sites.

In three acute experiments, recordings were made of pressures of the carotid artery, the right auricle (by means of a catheter inserted through the jugular vein), and the femoral vein through mercury manometers.

Two dogs were excluded from the series, one because it died of peritonitis postoperatively, and the other because the occluding suture was removed after one hour. The latter dog will be discussed briefly in the Early Fatalities section.

RESULTS

Of the forty dogs included in this series, eight died within a few hours after caval occlusion with a syndrome simulating phlegmasia cerulea dolens. Seven dogs died from other causes; three from anesthesia, two following venography (probably from too much Diodrast), and two from intercurrent disease.

Early Fatalities.—The eight deaths referred to previously as simulating phlegmasia cerulea dolens occurred within eighteen hours, and usually within four to eight hours, after ligation. The course of each was similar. Swelling, cyanosis, and coolness were evident in the lower extremities, scrotum, and lower abdominal wall, indicating a pooling of blood in these areas. The femoral vein pressures remained elevated (Fig. 2), and the animal died in shock of an oligemic type. These findings suggest that circulatory failure resulted from the inadequacy of the venous return from the areas distal to the caval occlusion. At autopsy the inferior venae cavae and the iliac veins were usually free of thrombosis, but in two animals, extensive thrombus filled these vessels. The inferior vena cava and lower extremity veins were grossly distended. The femoral vein was usually thrombosed in the area previously punctured. In several, the urine was grossly bloody, and small punctate areas of hemorrhage were seen in the low abdominal wall, bladder, and thighs. Pulmonary emboli were absent.

*Supplied by Winthrop-Stearns, Inc., New York.

Characteristic of the venous pressures in these dogs was a high venous pressure at the end of one hour (Fig. 2). In one dog, not included in this series, such a course was being observed, and it was felt that death was to be expected. At the end of fifty-five minutes the occlusion was removed. The venous pressure promptly fell to 35 cm. of saline solution, and the animal survived. When sacrificed one week later, the vena cava and its tributaries were normal.

Each of these eight early deaths was in a dog in which continuous femoral vein pressures were being observed. Four of them had received variable amounts of sodium citrate into the femoral vein, but the others had received only a few cubic centimeters of normal saline solution. The presence of a needle, or needles, in the femoral vein for from one to three hours was the only factor in common.

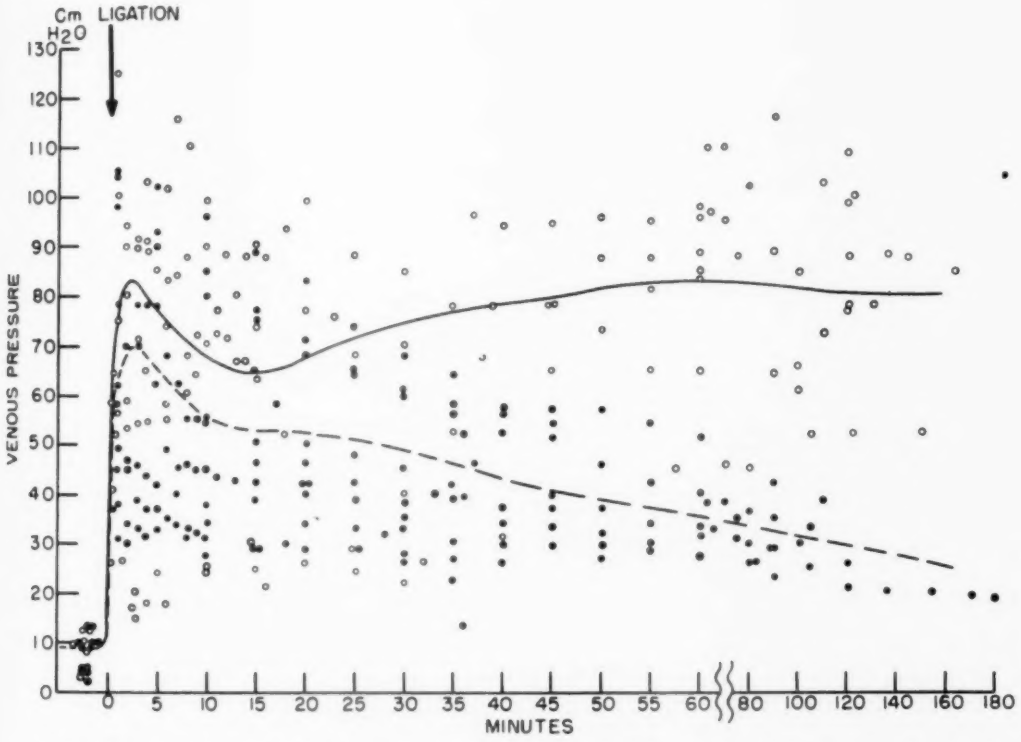


Fig. 2.—Immediate venous pressure response to occlusion of inferior vena cava in twenty-one dogs. ———— Average pressure response of the eight dogs which died (open circles). - - - - - - - - Average pressure response of the thirteen dogs which survived (solid dots).

Venous Pressures.—Continuous pressure observations before, during, and immediately following the occlusion of the inferior vena cava were made in twenty-one animals. The characteristics of the venous pressure response are seen in Fig. 2, which illustrates the difference in the response seen in the thirteen survivors from that of the eight fatalities. The almost immediate sharp rise in venous pressure was observed in both groups. The initial peak pressure, usually observed within the first minute or two, averaged 70 cm. of water in

the survivors and 84 in the fatalities. In the survivors, there was usually a rapid fall in pressure during the next few minutes, with a continued gradual decline during the next three hours. By the end of twenty-four hours the pressure had fallen only a few more centimeters, and no appreciable decrease occurred after the first day (Fig. 3).

The initial pressure averaged 8 cm. of water for twenty-one dogs (range 2 to 14 cm. of water), whereas the average pressure twenty-four hours to six months after occlusion was 15 cm. of water.

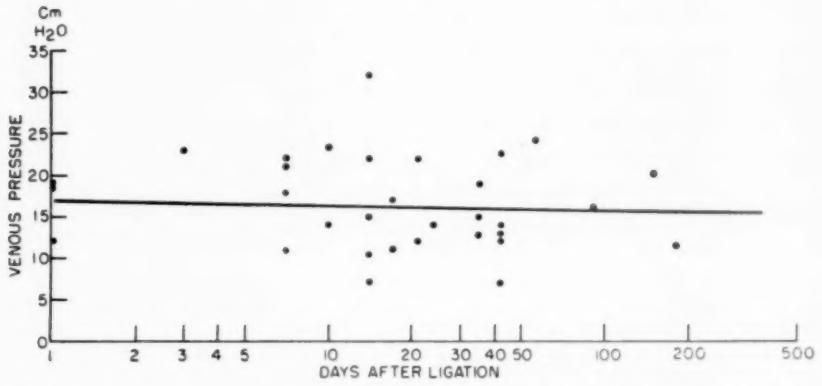


Fig. 3.—Late venous pressure response to caval ligation in twenty-three dogs. There is practically no decrease in femoral vein pressure after the first few hours.

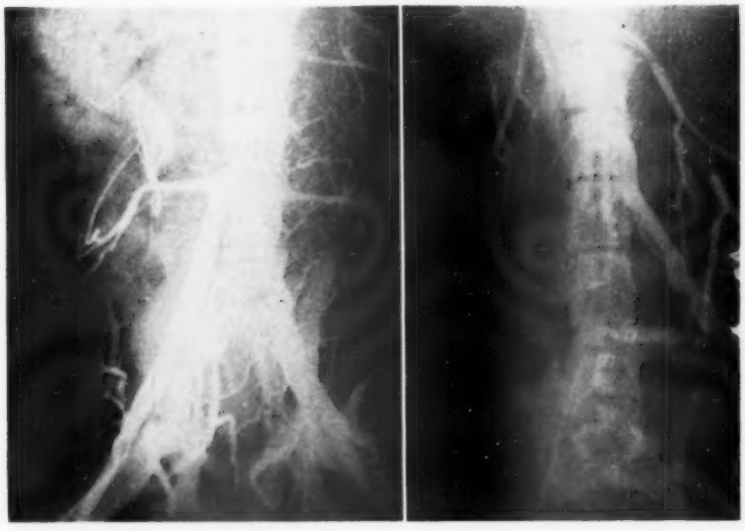
Of the ten aminals with some patency developing after removal of the occluding device, eight showed a drop in venous pressure ranging from 1 to 10 cm. of water. The average fall in these eight animals was slightly over 4 cm. of water, from an average of 19 to an average of 15 cm. of water.

Collaterals.—As evidenced by the early, rapid decrease in venous pressure, there is an almost immediate utilization of existing veins as collaterals through which the venous blood finds its way into the vena cava above the point of occlusion. If such collaterals do not develop soon and adequately, the animal dies, presumably from the shock which results from a pooling of blood below the caval occlusion. Our earliest roentgenographic evidence of collaterals was obtained by a venogram taken seventeen minutes after occluding the vena cava.

The earliest collateral pathways consist of an extensive network of very fine veins. At two weeks, most of the fine network of small veins has disappeared, and the collateral pathways consist of fewer but larger veins, chiefly the paravertebral plexus, the hemorrhoidal veins, and frequently the anterior abdominal wall veins. Changes continue in the same direction but more slowly, the collaterals eventually consisting of a few large veins with a variable number of smaller veins near the site of occlusion. Various stages in this development were seen in venograms taken at different intervals after occlusion. The early and late forms of collaterals are illustrated in Fig. 4. These impressions were substantiated by the gross findings of secondary operations and autopsies.

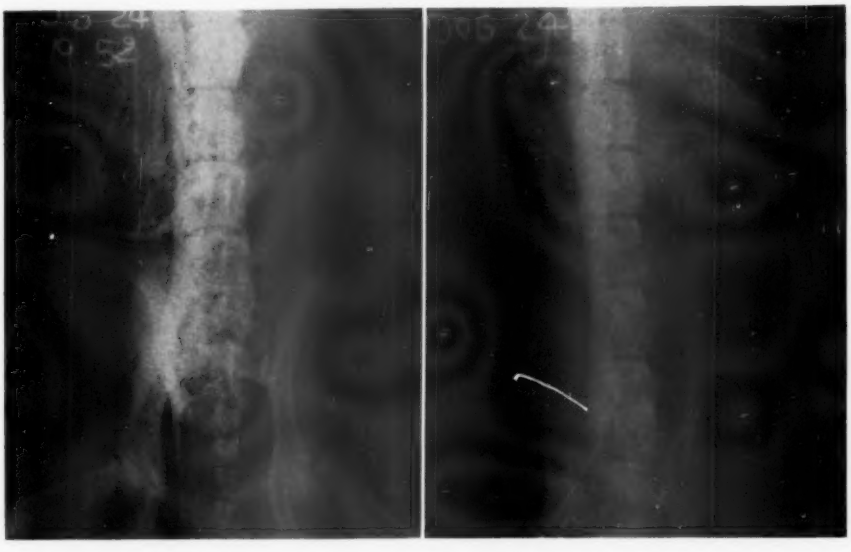
What happens to the collateral veins when the patency of the inferior vena cava is restored? Commonly, if an appreciable degree of patency is

restored, the collateral pathways shrink in size until they no longer function as collateral veins. This disappearance of the collateral pathways was the usual finding in the ten dogs in which reopening of the vena cava was demonstrated. Figs. 5 and 6 illustrate this phenomenon.



A. *B.*

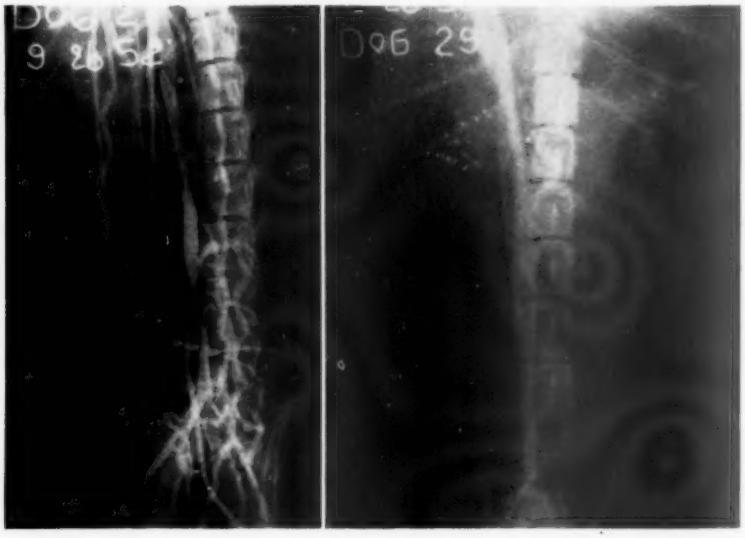
Fig. 4.—Very early and late forms of collaterals. (*A*, One hour after occlusion.) In *A* is illustrated the earliest form of collaterals, demonstrable within a few minutes after occlusion. (*B*, Six months after occlusion.) The late collaterals (*B*) develop within the first few weeks and show little change thereafter, as long as the caval occlusion persists.



A. *B.*

Fig. 5.—Reopening of vena cava and disappearance of collaterals. (*A*, Three weeks after removal of cotton tie.) In *A* the collaterals have already become smaller, even though the vena cava is only slightly patent. (*B*, Four months after removal of cotton tie.) In *B*, in the same animal, the degree of caval patency has increased considerably, and no collaterals are demonstrable.

Site of Occlusion.—Moderate fibrosis was evident about the site of occlusion with each type of occluding device. More scar tissue resulted with umbilical tape and collagen than with the No. 20 cotton or the clip. More total scarring occurred with the clip than with a cotton tie, but the lack of an annular scar about the vena cava after a clip was used allowed it to open more widely than after being tied with cotton.



A. *B.*

Fig. 6.—Reopening of vena cava and disappearance of collaterals. (*A*, Two weeks after removal of clip.) Many collaterals are visible in *A* when the caval patency is minimal. (*B*, Three and one-half months after removal of clip.) Three months later, in the same animal, the vena cava has opened more widely and the collaterals have ceased to function.

A thrombus developed just distal to the occlusion in many instances, as shown by venography and at autopsy. Ten of twenty-three dogs examined at intervals of more than two weeks after the beginning of the occlusion had old organized thrombus demonstrable in this area. There was no significant difference in this respect between those occluded by clip and those occluded by No. 20 cotton. The three occluded with umbilical tape showed no clot. In several instances, a very small, organized, and adherent thrombus found at autopsy had been demonstrated much earlier by venography as a large thrombus practically filling the vena cava distal to the occlusion. In two animals the vena cava distal to the occlusion was transformed into a very small, firm, "cordlike" structure. Most of the thrombi were small, completely organized, and firmly attached to one side of the vein wall, leaving an adequate lumen to the vein. Occasionally, a fine filament of fibrous tissue extended from the organized thrombus to the site of former occlusion.

Patency Regained.—Three animals were sacrificed immediately after removal of the occluding tie. No patency was demonstrable in two of these venae cavae tied with No. 20 cotton, whereas the third, occluded by umbilical tape, opened slightly just after the tape was removed. No lumen appeared in the one instance in which a collagen tie was used to occlude the vena cava, even after

four and one-half months. Twelve dogs were followed from one and one-half to four months after removal of the occluding mechanisms. Of these, ten regained some degree of patency, the openings ranging from 2 to 6 mm. in diameter, with an average of 3.8 mm. in diameter. Table I gives the relationship between the type of occlusion and the degree of patency regained.

TABLE I. RELATIONSHIP BETWEEN DURATION AND TYPE OF OCCLUSION, INTERVAL AFTER REMOVAL OF TIE OR CLIP, AND THE DEGREE OF PATENCY REGAINED

TYPE OF OCCLUSION	DURATION OF OCCLUSION	STATUS IMMEDIATELY AFTER REMOVAL OF TIE OR CLIP	DURATION OF FOLLOW-UP AFTER REMOVAL OF TIE OR CLIP	ULTIMATE DIAMETER OF LUMEN AT OCCLUSION SITE (MM. DIAMETER)
Tape	8 wk.	Occluded	11 wk.	4.5
Tape	6 mo.	Patent—3 mm. diameter	8 wk.	4
No. 20 cotton	7 wk.	Occluded	8 wk.	2
No. 20 cotton	7 wk.	Occluded	8 wk.	0
No. 20 cotton	9 wk.	Occluded	3½ mo.	2
No. 20 cotton	4 wk.	Occluded	6 wk.	3
No. 20 cotton	4 wk.	Occluded	4 mo.	6
Clip	7 wk.	Patent—3 mm. diameter	3½ mo.	4
Clip	7 wk.	Occluded	2 mo.	0
Clip	3 wk.	Patent—3 mm. diameter	4 mo.	4
Clip	3½ wk.	Occluded	3½ mo.	5
Clip	5 mo.	Occluded	7 wk.	4

The duration of occlusion bore no direct relationship to the degree of patency regained, but there was a larger lumen in those dogs followed for longer periods of time after removal of the tie or clip.

Fig. 7 shows a reopened vena cava seven weeks after removal of a clip.

Other Observations.—The three acute experiments with observations on arterial, right auricular, and femoral vein pressures were similar. Associated with the caval occlusion and the rise in femoral vein pressure was a slight, but definite, decrease in right auricular and arterial pressures. Fig. 8 shows this relationship, without the arterial pressure record. The arterial pressure decreased from 10 to 20 mm. Hg, beginning just after ligation. A few minutes later, coincident with a lower femoral vein pressure, the arterial pressure rose, and at the end of fifteen to twenty minutes it was within the normal range.

Further observations of interest were made in a dog which initially had shown the typical femoral vein pressure response with a peak of 78 cm. of water after caval occlusion. The clip was removed at the end of four weeks, during which time the collaterals became well developed. Eighteen weeks later, when the vena cava had reopened and the collaterals had disappeared, the vena cava was reoccluded. A venogram, taken ten minutes after reocclusion, showed well-developed, large collaterals without a fine meshwork. The venous pressure, which was 6 cm. of water prior to reocclusion, rose slowly to a level of 10 cm. of water in five minutes and remained at that level during the fifteen minutes of occlusion. These observations indicate that after the collaterals have once been well developed, they may develop more easily when again needed.

DISCUSSION

Fatalities.—Eight of the twenty-one dogs in which continuous venous pressure observations were being made died within a few hours from a lack of adequate venous return. No other dogs died with this complication. The only factor in common with these fatalities was the presence of a needle, or needles, in a femoral vein for from one to three hours. Soft thrombus in the area of the needle was usually observed within one hour or so. Balas and associates[9] demonstrated spasm of the collateral veins about the low thigh in dogs, induced by injecting thrombogen into a local segment of femoral vein. It is possible that the needles in, or the multiple punctures of, the femoral vein with the resulting thrombus may have reflexly produced spasm of the potential collateral bed. Such spasm could account for the inadequate venous return. The extensive thrombosis noted in two animals, although possibly secondary to venous stasis, probably contributed greatly to the failure of adequate collaterals to develop.

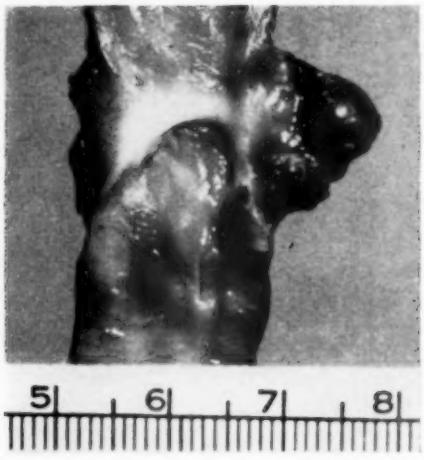


Fig. 7.—Dog 34. Vena cava seven weeks after removal of clip. Considerable narrowing is still present, although the opening measured 4 mm. in diameter. The polyethylene button, enclosed in a thin film of fibrous tissue, is seen just to the right of the constricted area. A tiny, well-organized thrombus is adherent to the wall just below the constricted area.

Again, we emphasize that only in dogs having continuous venous pressure observations was this lack of adequate collaterals noted.

Such a failure to develop collaterals may occur in human beings, but it must be relatively rare. Several human beings in whom some of the earliest inferior vena cava ligations were performed died within a few hours of the ligation.[10] Billroth's patient (1895), in whom he ligated the inferior vena cava thinking it was a dilated renal vein, died within one hour. Ludner's patient, in whom the vena cava was ligated during a hysterectomy for carcinoma, died immediately following the operation. Goldman's patient, who was in very poor condition with pyonephrosis, died a few hours after ligation of the vena cava. Perhaps the caval ligation had nothing to do with the deaths of these patients. On the other hand, considering the fact that adequate fluid replacement was not possible

at that time, perhaps the lack of adequate venous return from the lower extremities was "the straw that broke the camel's back," contributing greatly to circulatory failure and death.

A patient recently under our observation at the Salt Lake General Hospital was thought to have exhibited a course compatible with such a phenomenon. He was a 66-year-old man with chronic lymphocytic leukemia whose vena cava was ligated for a thrombophlebitis which was progressive in spite of adequate anticoagulant therapy. A few minutes after caval ligation his blood pressure fell to 85/50 from a previous level of 110/75. Blood transfusions, vasoconstrictor drugs, and other intravenous fluids failed to promote more than a temporary improvement in his shock. Steep Trendelenburg position and wrapping of the lower extremities failed also to prevent death, in shock, eight hours and forty minutes after caval ligation. No autopsy was permitted. It is presumed that inadequate venous return contributed greatly to, and probably was wholly responsible for, his circulatory collapse. There was no evidence of a thrombus in the vena cava at operation, and auscultation and roentgenography revealed no evidence of a pulmonary embolus.

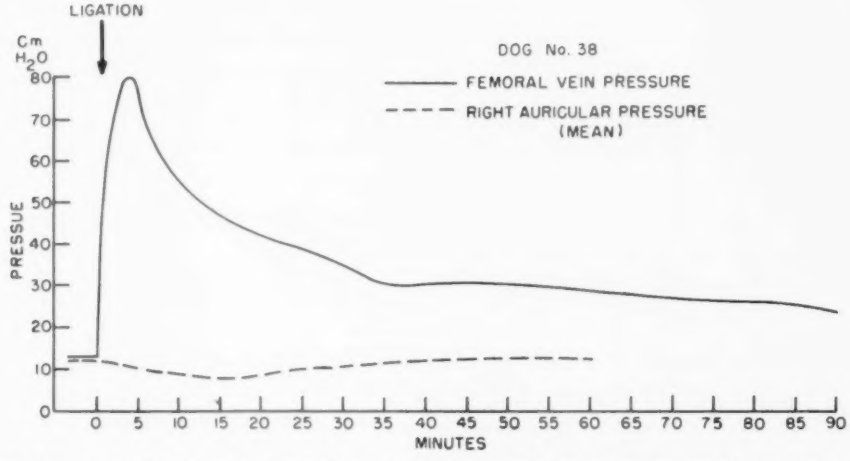


Fig. 8.—Typical pressure responses. Similar responses were recorded in three dogs by mercury manometer. The results have been translated into centimeters of water. Arterial pressure response is omitted from this reproduction (see text).

Some of the relatively few reported deaths occurring shortly after caval ligation and attributed to pulmonary infarction may instead have been due to inadequate venous return. Woodruff[11] observed a patient who developed profound shock following caval ligation but responded satisfactorily to the elevation and wrapping of his lower extremities with compression bandages. Buxton[12] observed another patient who, after ligation of the common femoral vein and an acute thrombophlebitis, developed syncope and hypotension. Circumferential measurements indicated a 2 L. loss of fluid into the extremity. He responded well to fluid replacement. Veal and associates[13] described a patient who developed massive venous occlusion a few minutes after a caval ligation, with venous distention, severe pain, cyanosis, and swelling of the extremities and hypotension. Recovery followed elevation and exercises of the affected extremity and blood transfusion.

Such occurrences must be rare, however, and should not contraindicate ligation of the vena cava if needed.

Venous Pressure.—Northway and Buxton[3] stated that in each of their ten patients the venous pressure of the lower extremities remained elevated. Subsequent reports by Ray and Burch,[14] Shea and Robertson,[7] and Collins and co-workers[1] leave no doubt that some degree of elevated venous pressure is the usual finding after caval ligations in human beings.

We have found no previous reports on the immediate pressure changes following occlusion of the inferior vena cava. Nabatoff and associates[15] found the venous pressures in the lower extremity "immediately after operation" to be three to four times the normal level. They apparently missed the early peak of the venous pressure rise which usually occurs within the first few minutes of occlusion and reaches a much higher level. They also stated that in no dog was a significantly elevated venous pressure present after the third postoperative day. Our observations indicate an average venous pressure, post caval occlusion, of 15 cm. of water after the day of operation, as compared to an average normal pressure of 8 cm. of water. Although we observed no ill effects of this degree of venous pressure from the standpoint of edema and interference with the function of the legs, this may still represent a "significant" elevation of pressure. It is assumed that the veins in the experimental animals were normal prior to caval occlusion, whereas in the human beings subjected to caval ligation, at least some of the veins below the ligation are abnormal in that they harbor thromboses.

Is it not possible, in the presence of pre-existing venous pathology, that increased venous pressure may result in an increased tendency toward the recurrence or persistence of venous thrombosis? Alexander[16] has demonstrated that there is a slight increase in the volume of venous blood in the lower extremity of the dog, in vivo, when the venous pressure is increased. A slightly increased vein diameter would decrease the rate of blood flow through a given vein and thereby increase the tendency toward spontaneous intravenous thrombosis.

Venous pressures following reopening of the vena cava decreased an average of 4 cm. of water. Why should there have been any decrease in venous pressure unless the previous increased pressure were of some significance? Slight changes in pressure can exert a profound influence on the veins. Evidence of this is the disappearance of large collateral veins as the vena cava reopened and as the venous pressure decreased.

COLLATERALS

The collateral circulation of the inferior vena cava in human beings has been thoroughly studied in recent years by injection studies of adult cadavers[3] and stillborn infants,[17] venograms obtained immediately after occlusion of the vena cava,[18] and observations on patients previously subjected to caval ligation.[3]

Venographic studies of the collaterals in dogs have been reported by Nabatoff and co-workers[15] and Streuter and Paine.[8]

Our observations indicate that there is, within a matter of minutes, an extensive collateral system consisting of a very fine network of small veins. This extensive network rapidly changes, by enlargement of the more direct pathways and by a return toward normal of the less direct routes, into a less extensive, but more direct, system of large veins. Late observations revealed less anterior abdominal wall vein enlargement than was present earlier, perhaps signifying that as the more direct pathways became larger and more adequate, the less direct pathways became less needed and consequently diminished in size. Similar observations have been reported by Balas and associates[9] in relation to collaterals of the dog's lower extremity.

Routinely, as the vena cava regained its patency, the size of the collateral pathways decreased and, in some, all venographic evidence of collaterals disappeared. Streuter and Paine[8] implied that this was true in their experiments also. This observation is against the contention that the persistent increased venous pressure is without detriment to the host. If the collaterals were as physiologic as the normal vena cava, no change in the collaterals and no reopening of the vena cava would be expected when the occluding device was removed from the vena cava. Yet, the vena cava did reopen, and the collaterals did shrink and cease to function as collaterals. Some increased pressure must be required to hold the collaterals open. Since the collaterals respond so dramatically to small changes in venous pressure, significant changes in the veins of the lower extremities may also be expected. And these changes in the lower extremity veins may be instrumental in promoting thrombosis and the "undesirable sequelae" observed after caval ligation.

Method of Occlusion.—One requirement for a temporary occlusion of the vena cava should be that the occlusion will persist for as long an interval as desired prior to allowing the vena cava to reopen. The occlusion should probably be for a longer period than would be afforded by a catgut tie. The use of a clip, a tie of No. 20 cotton, or umbilical tape will assure the occlusion for as long as desired, and when no longer needed, their removal will usually allow the vessel to reopen. A stainless steel clip is preferable since it can be removed easily with less danger of injuring the vena cava, and probably with a better chance of future caval patency. It is probable that the clip can be removed without a major operation simply by nicking the skin and pulling on the attached suture. If the pull-out suture breaks, operative exposure and removal of the clip will be required, but this would still be technically easier and less hazardous than the dissection and removal of a ligature. The position of both the clip and the button can be checked roentgenographically since each contains radiopaque material.

The possible danger of embolism from the thrombus which may form distal to the occlusion is probably eliminated by leaving the clip in place until organization or dissolution has occurred. Should reopening of the vena cava occur within a period of two to three weeks, as it may do if occluded by a catgut tie, the danger from this source would seem to be greater. In one dog sacrificed two weeks after occlusion, a large thrombus, not firmly adherent to the intima, was found filling the vena cava just below the occlusion. Such a thrombus was not found in these studies later than two weeks after occlusion. The presence of a large thrombus can be detected by venograms in dogs and, it is assumed, in the human being. It may be desirable to visualize this area venographically prior to removing the clip, although there should be no danger from this source if the clip is not removed within the first two months.

SUMMARY AND CONCLUSIONS

Many patients who have had a ligation of the inferior vena cava develop undesirable sequelae. These sequelae may be the result of persistent, or recurrent, venous pathology rather than the direct result of caval ligation. It is postulated that, through a slowing of the venous blood flow, caval ligation may predispose to venous pathology and thereby indirectly produce the undesirable sequelae.

Because caval ligation may be undesirable as a permanent state, even though sometimes indicated as a lifesaving measure, this study was undertaken to investigate various means of occluding the vena cava temporarily.

The inferior venae cavae of forty dogs were occluded by ligatures or by stainless steel clips. Observations were made on the resulting venous pressures and collateral veins.

Eight dogs in which venous pressures were being observed continuously developed pooling of blood in the lower areas of the body due to inadequate venous return, with resulting shock and death. Characteristic of their venous pressures was a very high initial peak and a failure to recede normally during the following hour.

The immediate venous pressure response in the survivors was also characterized by a high peak within one or two minutes but with a rapid fall to a level of 30 to 40 cm. of water by the end of one hour. No appreciable decrease in the postocclusion venous pressures of survivors was observed after the first few hours. Twenty-four hours after occlusion, and up to six months later, the average venous pressure was approximately 15 cm. of water. The initial, preocclusion average pressure was 8 cm. of water.

Venographically, it was demonstrated that the collaterals develop almost immediately as an extensive meshwork of fine veins. By an enlargement of the more direct collateral pathways and a disappearance, or shrinkage, of the remainder of the extensive meshwork, the collaterals are grossly altered within the first few weeks. Ultimately, relatively few, large, and fairly direct pathways comprise the collateral system.

Ten of the twelve dogs which were followed for one and one-half to four months after removal of the occluding device regained some degree of patency. The size of the new opening averaged 3.8 mm. in diameter, the larger openings being in those dogs with longer periods of follow-up.

Associated with the reopening of the vena cava and the slight fall in venous pressure, the collaterals usually decreased in size until they were no longer visible roentgenographically.

A metal clip is probably superior to a ligature as a means of producing temporary occlusion. Such a clip may be left in place to produce a permanent occlusion of the inferior vena cava. Should undesirable sequelae develop to which the caval occlusion may be contributing, the clip may be removed with excellent prospects that the vena cava will regain its patency.

Temporary occlusion of the inferior vena cava deserves serious consideration as a means of preventing pulmonary embolism.

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DISCUSSION

DR. EARLE B. MAHONEY (Rochester, N. Y.).—Your results in general agree very closely with Dr. Dale's. I would like to ask you a question. What do you think of using catgut as a temporary ligature?

DR. MAX TAFFEL (New Haven, Conn.).—Neither the speaker yesterday nor the one today seemed to be particularly concerned about the possible late development of a thrombus in the veins distal to the site of the application of the ligature. They have demonstrated that ligation of the vena cava leads frequently, even in an animal with presumably normal veins, to the development of thrombi and to thickening and narrowing of the distal veins. Such areas of thickening and narrowing will of course impede the free flow of blood in these veins and may in themselves be responsible for new thrombi at some later date. The patient in whom ligation of the vena cava is contemplated or performed has already demonstrated his inherent tendency, little understood though that may be, to develop dangerous thrombi. The additional thickening and narrowing of the veins must, it seems to me, seriously abet the tendency to thrombosis which the patient has already demonstrated to be present in more than ample measure. Having therefore increased the chances of thrombosis by the ligation, I think I should prefer to make that ligation as permanent as possible, and not allow the vena cava to open again and thus provide the damaged peripheral vessels once again with a free and open venous highway to the lungs.

DR. W. A. DALE (Rochester, N. Y.).—This is certainly a point to be considered. The series of animals upon which we reported yesterday were normal animals with normal veins.

As yet we have had no clinical experience, as the only patient for whom the operation was proposed, unfortunately, died before it could be performed. We hope to test the effects of anticoagulants on the prevention of the thrombosis which occurred distal to the ligature site in our animals. Our experimental evidence indicates that, although a clot does form distal to the site of vena caval ligation, at the time the cava becomes deligated this thrombosis is well organized and firmly attached to the venous wall. There have been no instances of loose or soft elements found.

DR. MORETZ (Closing).—I agree with Dr. Dale's comments.

The question was raised as to whether a catgut ligature may be preferable to the clip which we have mentioned. Patients who require caval occlusion may be considered in two separate groups. The first group includes those in whom a pulmonary embolus occurred while the patient was fully ambulatory and without preceding illness. There is little possibility in this group of being able to change the environment to such an extent that a recurrence of thrombosis and the possible dangers of embolism can be prevented. Therefore, a permanent form of caval occlusion is probably advisable for this group.

The second and larger group includes those in whom a caval occlusion is indicated because anticoagulants were either contraindicated or ineffective. These individuals have been ill and inactive. Following their recovery and return to active life, one would not expect new thrombi to form. For this group, there might be a place for temporary occlusion of the vena cava.

I prefer the clip over a catgut ligature. The time of reopening is more predictable and can be varied more accurately with a clip. Also, if the occluded vena cava is producing no sequelae, one may elect to leave it occluded, whereas, with a catgut tie, reopening will probably occur whether or not you wish the occlusion continued. When a clip has been used, you can change your mind and leave it on, but with a catgut ligature you are committed to a temporary occlusion.

Dr. Taffel's remarks are well taken, as Dr. Dale has indicated. However, except for the first two weeks after caval occlusion, we did not see a thrombus distal to the point of occlusion which appeared capable of breaking off and forming an embolus. Those seen after one to three months were uniformly small, well organized, benign appearing, and quite adherent to the vein wall.

AN EVALUATION OF JEJUNAL AND COLIC TRANSPLANTS IN EXPERIMENTAL ESOPHAGITIS

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(From the Department of Surgery, the Ohio State University Medical School)

AT PRESENT there is no general agreement on a satisfactory method of treating chronic peptic esophagitis. This lesion is usually the result of an inherent or surgically produced abnormality of the cardia mechanism which permits gastric secretions to reflux into the esophagus.[1, 2] The esophageal mucosa is so vulnerable to gastric secretions that peptic esophagitis readily occurs in persons with normal gastric acid values as well as in individuals with an ulcer diathesis.[3-5] This susceptibility of the esophagus has been recently emphasized in the work of Arroyave and associates,[6] who produced esophagitis in dogs by sewing a small pedicled patch of gastric mucosa into a window in the esophageal wall. In cases where medical management and esophageal dilatation have failed, various surgical procedures have been employed. These include near-total gastric resection,[5] posterior gastroenterostomy with vagotomy,[7] and stomach by-pass operations which connect the esophagus directly to proximal jejunum.[1, 8, 9] Such operations have one or both of the following disadvantages: (1) gastric and esophageal mucosa are left in continuity without restoring the cardia sphincter mechanism, or (2) gastric function is sacrificed.

It is the purpose of this paper to report the results of an experimental method devised for the treatment of chronic peptic esophagitis. This method prevents gastric juice from eroding the esophagus, preserves normal gastric function, and maintains essentially normal functional continuity of the alimentary tract.

EXPERIMENTAL METHOD

These experiments were carried out in dogs in which the cardia mechanism was destroyed, and a segment of jejunum or colon, with the vascular pedicle intact, was used as a bridge between the esophagus and the stomach. Unlike esophageal replacement procedures, in which long segments of intestine are needed,[10, 11] the method to be reported here deals with comparatively short segments placed between the esophagus and stomach for the purpose of separating the mucosa of these two organs and of providing a sphincterlike mechanism at the inlet of the stomach. An evaluation was made of the relative tolerance of these two types of pregastric intestinal grafts to gastric juice in normal and in histamine-stimulated dogs.

Operative Procedure.—(Fig. 1.) Twenty-one adult mongrel dogs were operated upon, of which fifteen recovered for evaluation. Three types of operative procedures were performed in these dogs: (1) resection of the distal esophagus and cardia with esophagojejunogastrostomy, (2) resection of the distal esophagus and cardia with esophagocologastrostomy, and

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(3) resection of the distal esophagus and cardia with esophagogastrostomy. Included in the third group is one dog in which a hiatus hernia was produced. This third group constituted the control series.

Intravenous pentobarbital sodium was used for induction of anesthesia, supplemented with endotracheal ether and oxygen. The chest was opened through the left eighth intercostal space and the incision continued across the upper abdomen to the midline. The diaphragm was incised to the esophageal hiatus. Five centimeters or less of the distal esophagus and the cardia was resected and the stomach closed. In all instances the vagi were carefully preserved.

Group 1.—Jejunal transplants: In five dogs, a segment of jejunum, 8 to 16 cm. in length and just distal to the ligament of Treitz, was chosen for transplantation. A suitable vascular arcade, usually the third or fourth, was chosen to supply the implanted segment. By incising the mesentery on either side parallel to the blood vessels, sufficient pedicle length could easily be obtained. In all instances, viability of the transplanted segment was maintained. The bowel was divided between clamps and, after closing each end of the transplant, intestinal continuity was restored by end-to-end jejunojejunostomy and the mesentery carefully reapproximated. The transplant was passed through a rent in the transverse mesocolon, behind the colon and the stomach, and into the chest, where it was placed in an isoperistaltic position. Particular care was taken to avoid twisting the vascular pedicle. Proximally, the esophagus was anastomosed end to side to the jejunal segment and, distally, a generous side-to-side jejunogastrostomy at the fundus was performed. The rent in the transverse mesocolon was carefully closed. All anastomoses were accomplished in two layers with interrupted 0000 black silk sutures.

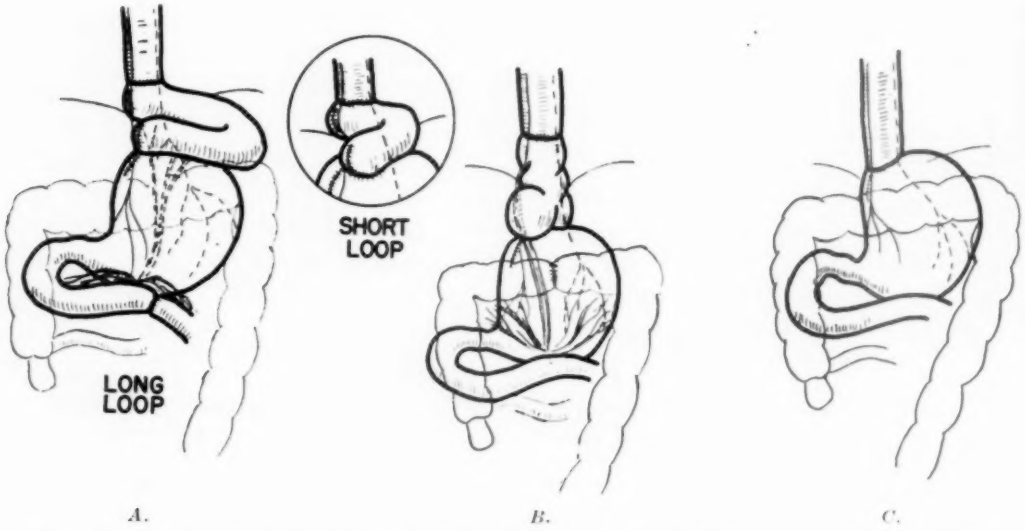


Fig. 1.—*A*, Jejunal transplant; *B*, colic transplant; *C*, esophagogastrostomy (control).

Group 2.—Colic transplants: Five dogs were prepared with neomycin (1 Gm.) and castor oil (0.5 ounce) daily for three days prior to operation. Transplants, 10 to 15 cm. in length, were taken from the transverse colon using the middle colic vessels as the vascular pedicle. The procedure was essentially the same as the one described for the jejunal transplants, except that an end-to-end anastomosis was made with the esophagus and an end-to-side was made with the fundus.

Group 3.—Control group: In the third group, the cardia and lower few centimeters of the esophagus were resected in four dogs. The cardia was sutured closed, and an end-to-side esophagogastrostomy was performed at the fundus. In a fifth dog, a hiatus hernia was produced by incising the esophageal hiatus, drawing 25 per cent of the stomach through the diaphragm into the chest, and suturing it securely in this position.

TABLE I. TRANSPLANTATION OF JEJUNAL SEGMENTS BETWEEN ESOPHAGUS AND INTACT STOMACH

DOG NO. WEIGHT (KG.)	LENGTH OF IMPLANT (CM.)	BEFORE HISTAMINE STIMULATION					AFTER HISTAMINE STIMULATION			AUTOPSY FINDINGS		
		P.O. WEIGHT TREND	P.O. EATING HABITS	Hb. Hct. P.O. DAY	ESOPHAGOSCOPY FINDINGS	FLUOROSCOPY FINDINGS	DAY P.O.	CHANGE IN BEHAVIOR	DAYS TO DEATH	STOMACH AND DUODENUM	TRANSPLANTED LOOP	ESOPHAGUS
15L 14.2	12.5	Gained 15.4	Moist food taken well; dry bread regurgitated; no vomiting	15.7 56 86	No esophagitis; anastomosis visualized (98 days P.O.)	No reflux; no obstruction (93 days P.O.)	165	Eating much less, no vomiting	18	Grade III 1 cm. ulcer in duodenum	Grade I in distal 1 in. and 2 linear Grade III ulcers at stoma	Intact
11L	15.0	Maintained well	Moist food taken well; dry bread regurgitated; no vomiting	17.7 62 100	No esophagitis; unable to enter jejunal loop (112 days P.O.)	No reflux; no obstruction (107 days P.O.)	142	Refusing most of food, no vomiting	5	Grade II 0.2 by 0.2 cm. ulcer	Grade I 2.1 by 1 cm. erosions at gastric stoma	Intact
27L 15.4	8.0	Maintained well	Moist food taken well; dry bread regurgitated; no vomiting	12.7 54 91	No esophagitis; no jejunitis (66 days P.O.)	No reflux; no obstruction (96 days P.O.)	95	No change in eating habits, no vomiting	39	Grade III antral ulcer 1.5 cm., Grade II duodenal ulcer 0.5 cm.	Intact	Intact
13L 12.2	5.0	Gained and held 14.2	Both dry and moist food eaten without regurgitation	12.5 49 98	No esophagitis; no jejunitis; one suture line granulation (43 days P.O.)	Reflux present; no obstruction (103 days P.O.)	103	Eating less, some tarry vomitus	15	Grade II antral gastritis	Grade II ulcer at gastric stoma	Grade III generalized erosion with hemorrhage
13U 11.3	4.0	Maintained well	Moist food taken well; refused dry bread	14.5 49 70	No esophagitis; no jejunitis (82 days P.O.)	No reflux demonstrated (77 days P.O.); no obstruction	145	Refusing most food, tarry vomitus	3	Grade III antral ulcer, small duodenal ulcer	Grade I erosion of gastric stoma	Grade IV generalized erosion with hemorrhage

TABLE II. TRANSPLANTATION OF COLON SEGMENTS BETWEEN ESOPHAGUS AND INTACT STOMACH

DOG NO. WEIGHT (KG.)	LENGTH OF IMPLANT (CM.)	BEFORE HISTAMINE STIMULATION					AFTER HISTAMINE STIMULATION			AUTOPSY FINDINGS		
		P.O. WEIGHT TREND	P.O. EATING HABITS	Hb. Het. P.O. DAY	ESOPHAGOSCOPY FINDINGS	FLUOROSCOPY FINDINGS	DAY P.O.	CHANGE IN BEHAVIOR	DAYS TO DEATH	STOMACH AND DUODENUM	TRANSPLANTED LOOP	ESOPHAGUS
19U 11.1	10	Maintained well	All food taken well	—	No esophagitis; anastomosis seen (45 days P.O.)	—	49	Refused most food, tarry vomitus	3	Grade II antral gastritis with bleeding	Grade II generalized ulceration without histologic inflammation (probably post-mortem)	Intact
27U 10	7	Gained 11.3	All food taken well	12.1 43 21	No esophagitis; colon loop visualized intact (33 days P.O.)	—	63	Refused most food	3	Grade II ulcer 0.5 cm.	Grade V large perforation	Intact
22L 14.2	7	Gained 15.9; looks fat	All food taken well	—	No esophagitis; anastomosis seen (38 days P.O.)	Reflux present (61 days P.O.)	83	No change in habits, no vomiting		Grade II gastritis with bleeding	Grade II generalized erosion	Grade II generalized erosion
26L 15.2	7	Decreased to 14.2; failed to gain	Intermittently refused food, no vomiting	15 7 55 23	No esophagitis; colon loop intact (86 days P.O.)	—	—	None	Sacrificed 86 days P.O.	Intact	Intact	Intact
28L 16.8	10	Maintained well	All food taken well	—	No esophagitis; colon loop intact (35 days P.O.)	No reflux	—	None	Sacrificed 84 days P.O.	Intact	Intact	Intact

TABLE III. RESECTION OF CARDIA AND ESOPHAGOGASTROSTOMY OR HIATUS HERNIA (CONTROL SERIES)

DOG NO. WEIGHT (KG.)	BEFORE HISTAMINE STIMULATION				AFTER HISTAMINE STIMULATION			AUTOPSY FINDINGS		
	P.O. WEIGHT TREND	P.O. EATING HABITS	Hb. Hct. P.O. DAY	ESOPHAGOSCOPY FINDINGS	DAY P.O.	CHANGE IN BEHAVIOR	DAYS TO DEATH	STOMACH	DUODENUM	ESOPHAGUS
3U 10.6	Maintained well	Takes all food well, no vomiting	13.1 14.7 56	Superficial linear erythema Grade I (31 days P.O.)	61	Tarry stools, occasional vomiting; esophagoscopy generalized Grade II esophagitis 7 days after histamine	Sacrificed at 16 days	Intact	Grade II 3 cm. ulcer	Grade IV 5 cm. ulcer just above gastric stoma
17U 10.9	Gained 16.8; looks fat	Takes all food well, no vomiting	13.5 48 42	Grade I superficial generalized erythema, slight bleeding (17 days P.O.)	47	No change in eating habits; esophagoscopy 33 days after histamine ulcer above gastric stoma	42	Intact	Grade II 1 by 1.5 cm. ulcer	Grade V perforation above gastric stoma, generalized Grade III esophagitis
25L 12	Maintained slight gain	Takes all food well, no vomiting	14.7 44 35	Grade II ulcer above gastric stoma (98 days P.O.)	110	Eating less	14	Intact	Grade II small ulcer	Grade III generalized esophagitis with hemorrhage
4L 15.4	Maintained slight gain	Takes all food well, recurrent mucoid vomiting	11.5 41 43	Grade II ulcer above gastric stoma (80 days P.O.)	118	Eats well but daily vomits mucus				
16L 12.5	Maintained at operative level	Eats well but recurrent mucoid vomiting	12.5 43 62	Grade I superficial erythema (74 days P.O.)	137	Eats well but daily vomiting more severe, mucoid	9	Intact	Grade II small ulcer	Grade II superficial linear generalized erosion

In all three groups, the diaphragm was closed snugly around the stomach or the transplanted limb of intestine, care being taken not to compromise the vascular pedicle. In some instances, it was possible to close the mediastinal pleura over the graft. (For anatomic reasons, this would be more readily accomplished in patients and would be properly accompanied by extrapleural mediastinal drainage.) The thoracoabdominal incision was closed in layers, using interrupted silk technique throughout.

There were three deaths due to technical failures associated with leakage at the proximal suture line, and one due to acute gastric dilatation (possibly associated with trauma to the vagi). There were two deaths due to distemper.

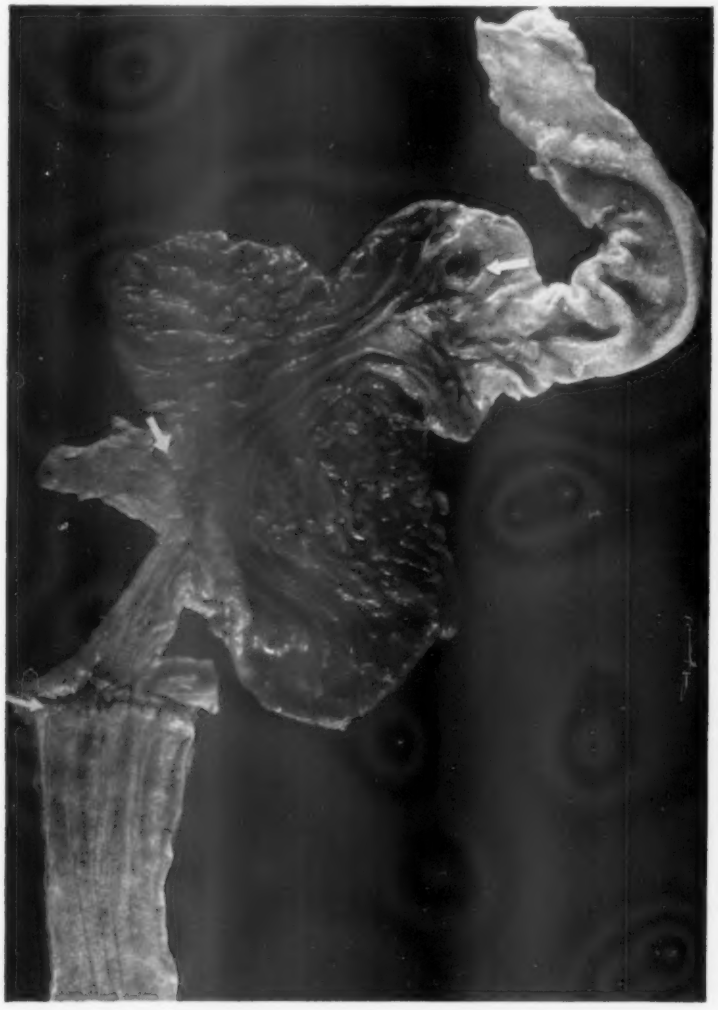
A.

Fig. 2.—*A*, Dog 17U. Esophagogastrostomy; dog died of perforated esophagus on forty-second day of histamine stimulation. Arrows indicate point of perforation. Grade III duodenal ulcer present.

All the other dogs were allowed to convalesce fully from the operation. Their eating habits were observed carefully, and fluoroscopic studies were made on representative animals. Esophagoscopic examinations were performed on every dog. After a period of observation, varying from forty-seven to 165 days, thirteen of the dogs were placed on 30 mg. histamine-beeswax* daily. As each dog died, the intact specimen, consisting of esophagus, transplant,

*Provided through the courtesy of Hoffmann-La Roche, Inc., Nutley, New Jersey.

stomach, and duodenum, was removed, photographed, and preserved by freezing. The gross and histologic pathologic findings were graded according to the classifications of Dameron and Wangensteen[12]: Grade I, slight necrosis of the mucosa; Grade II, necrosis extending to submucosa; Grade III, necrosis of the mucosa with extension into muscularis; Grade IV, near perforation (extension to serosa); Grade V, perforation.



B.

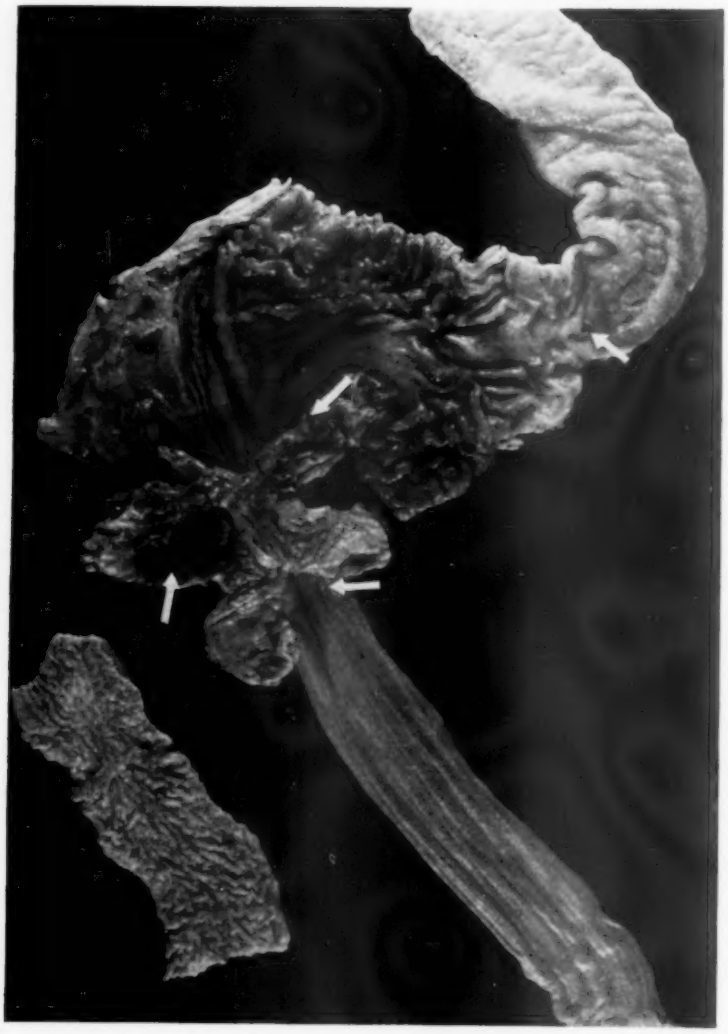
Fig. 2.—*B*, Dog 271. Jejunal transplant, 8 cm. in length, after thirty-nine days of histamine stimulation. Esophagus and jejunal loop are intact. A large deep antral ulcer is present.

RESULTS

The dogs were evaluated before and during histamine stimulation; that is, during an interval when gastric secretion was presumably normal and then during a period when an "ulcer diathesis" was artificially created. Results are presented in Tables I, II, and III.

All the control dogs with simple esophagogastric anastomosis and the one with hiatus hernia spontaneously developed Grade I or II esophagitis before

histamine stimulation. This is in keeping with the experience of others.[13-16] In the other dogs, both the jejunal and colic transplants tolerated being in direct contact with the fundus of the stomach. Before histamine stimulation was started, there was no erosion or inflammation visible at esophagoscopy in any of these intestinal segments or in the esophagus.

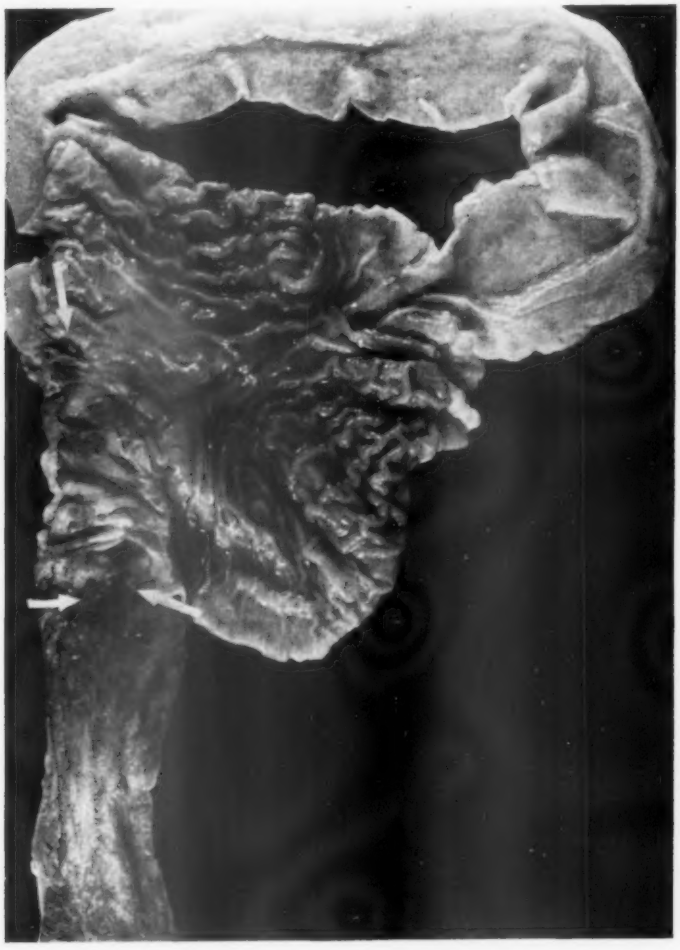


C.

Fig. 2.—*C*, Dog 27U. Colon transplant, 7 cm. in length, after only three days of histamine stimulation. A small duodenal ulcer is present as well as the large perforation in the colon loop. Esophagus is intact.

Following histamine stimulation, severe esophageal erosion and perforation developed in the control series (Fig. 2, *A*). In the dogs with intestinal transplants, erosion developed in both types of transplants in the area of the gastric anastomosis, whereas the proximal portions of the transplanted limbs and the esophagus itself were free of pathologic change (Fig. 2, *B* and *C*). These

histamine-induced lesions in the intestinal transplants were accompanied by similar pathologic findings in the stomach or duodenum. Exceptions did occur in three dogs. In these animals, in which fluoroscopy had previously demonstrated reflux into the esophagus, esophagitis appeared after histamine stimulation. Two of the dogs had jejunal transplants, which at autopsy were less than 5 cm. in length. A third dog had a colon transplant 7 cm. in length. In all three of these animals there were deep esophageal ulcerations which resulted in death from hemorrhage. The intestinal segments themselves were also eroded (Fig. 2, *D*).



D.

Fig. 2.—*D*, Dog 13L. Jejunal transplant, 5 cm. in length, after fifteen days of histamine stimulation. There is a generalized Grade III esophagitis present with the jejunal loop showing a small very superficial erosion at the gastric stoma. Arrows indicate the suture lines.

DISCUSSION AND CONCLUSIONS

There are numerous clinical and experimental reports which provide information regarding the resistance of transplanted intestinal mucosa to stomach secretions. Kay[17] has successfully anastomosed jejunal segments to

stomach in esophageal replacement experiments. Ivy,[18] speaking from his own experience and reviewing the work of others, has concluded that the jejunal mucosa is well able to withstand continuous exposure to normal gastric content. Dragstedt and Vaughn[19] have similarly demonstrated this for colon. Roux[20] was the first to anastomose a jejunal transplant directly to the stomach in patients. More recently Swenson,[21] Harrison,[22] and Leven and Varco[23] have had occasion to anastomose jejunal segments to the stomach while performing esophageal replacement operations for the correction of acquired lye stricture or congenital esophageal atresia. They did not note ulcerations of the jejunum. Ravitch[24] has described similar successful results in infants, but he stated that jejunal ulcerations have developed in two adult cases of antethoracic esophagoplasty for lye stricture. Battersby[25] has reported an experimental and clinical study in which colon replacement for esophagus showed the gastrocolic anastomosis to be well tolerated.

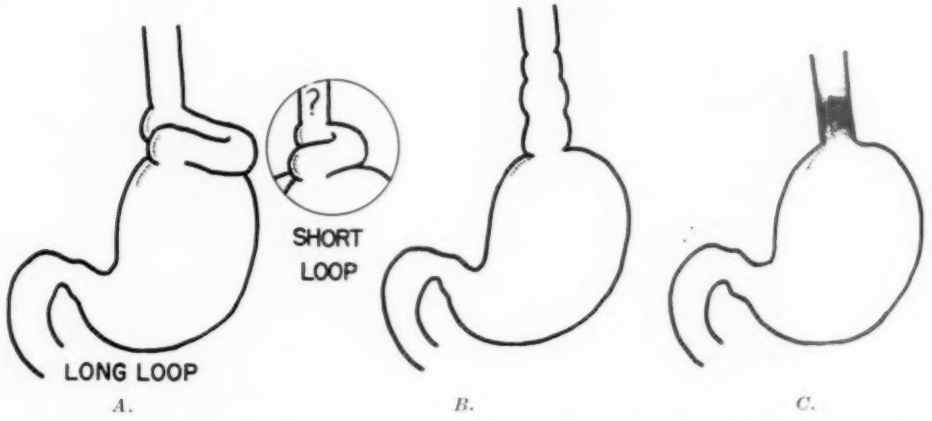


Fig. 3.—Before histamine. *A*, Jejunal transplant; *B*, colic transplant; *C*, esophagogastrostomy (control).

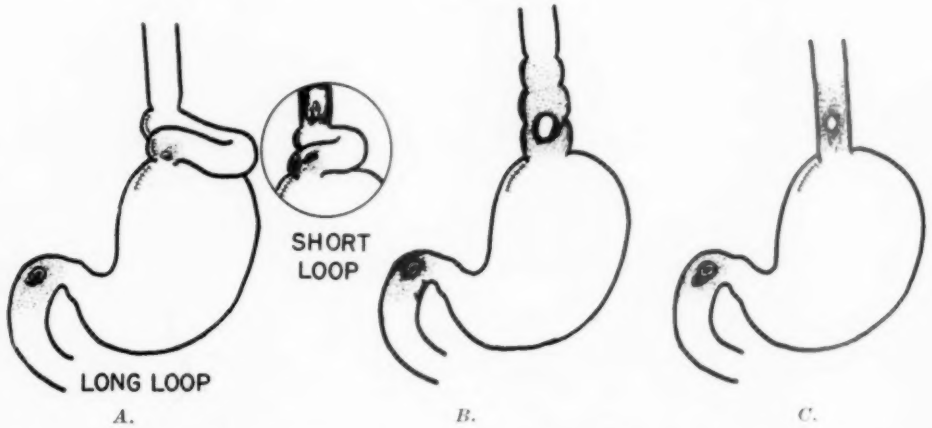


Fig. 4.—After histamine. *A*, Jejunal transplant; *B*, colic transplant; *C*, esophagogastrostomy (control).

It was our impression, gained from daily observations of the dogs and from information gained during fluoroscopy, that the colon transplants provided easier deglutition because of their larger diameter. In the jejunal preparations, the

barium meal passed into the stomach after being retarded somewhat by to-and-fro peristaltic action. These studies also indicated that there was no regurgitation from the stomach into the esophagus except in the three dogs previously described. In these three, two jejunal segments of less than 5 cm. and one colon segment of 7 cm. were too short to function effectively as a valve or artificial cardia.

Certain inferences may be drawn from these experiments which deserve emphasis because they may have a clinical application. The status of the patient with normal gastric secretion who develops reflux esophagitis because of an inherent abnormality, such as chalasia, achalasia, hiatus hernia, and congenital short esophagus, or because of an acquired abnormality, such as resection of lower esophagus and cardia or Heller-type procedure, is comparable to that of our unstimulated control dogs.[26] These patients invariably develop a degree of esophagitis which may be extremely resistant to medical treatment and eventually lead to recurrent hemorrhage or cicatrix formation and stenosis. Our work suggests that in such cases, a segment of jejunum or colon of adequate length may be safely implanted between the esophagus and the stomach and thus prevent esophagitis without fear of erosion occurring in the transplanted segment (Fig. 3).

Unfortunately, such segments, although providing protection for the esophagus, are unable themselves to resist erosion completely when exposed to excessive (histamine-induced) gastric secretions (Fig. 4). In a comparable situation in patients who have a well-established "ulcer diathesis," it might be feasible to employ an intestinal transplant if a procedure to reduce gastric acidity such as a partial gastrectomy[27, 28] or vagotomy and pyloroplasty (gastroenterostomy) were performed concomitantly.

SUMMARY

Loss of cardia function results in reflux of gastric secretions into the esophagus and the frequent development of peptic esophagitis. Because the esophageal mucosa is so vulnerable, this lesion may readily occur in individuals with normal gastric acid values as well as in those with an ulcer diathesis.

In a group of dogs in which the cardia mechanism was deliberately destroyed, both gastric reflux and its sequel, esophagitis, were prevented by interposing a transplanted loop of either jejunum or colon of adequate length, with its vascular pedicle intact, between the esophagus and the stomach.

Under normal conditions, contact with gastric secretions was found to be well tolerated by both jejunal and colic segments transplanted to the inlet of the stomach. When an "ulcer diathesis" was simulated by histamine stimulation, both types of transplanted segments were eroded (colon segments more than jejunum), yet the esophagus was protected from injury.

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DISCUSSION

DR. C. D. SHERMAN (Rochester, N. Y.).—Workers in the field of esophageal reconstruction have found from clinical experience that if jejunum is anastomosed to stomach, the frequency of jejunal ulceration at the jejunal gastric margin is so high that most now feel they should by-pass the stomach rather than anastomose jejunum in the stomach.

Dr. Sirak pointed out that most of these transplants in the past have been subcutaneous. Perhaps that makes some difference. I rather doubt that the placing of a jejunal transplant into the chest as opposed to placing it subcutaneously will make any difference in the incidence of jejunal peptic ulceration.

In all of the literature and in the few cases that we have learned about in recent years, there has not been reported any clinical incidence of ulceration of the colon at its anastomosis into the stomach.

Therefore, I feel perhaps a little bit more inclined to use the colon rather than the jejunum in the instances in which this procedure would be indicated.

DR. WILLIAM A. BARNES (New York, N. Y.).—I would like to inquire how often histamine was given, the duration and dosage, and what time interval elapsed before the changes in the esophagus and jejunum were noted.

DR. SIRAK (Closing).—To answer Dr. Sherman's query, we do not know for certain which is the better intestinal interposition to use, the jejunum or colon. Our work would suggest that the jejunum is a bit more resistant, but we cannot be sure.

In regard to Dr. Barnes's question, these animals were placed on 30 mg. of histamine-in-beeswax daily. Some of the intestinal transplants began to perforate in as short a time as three days, while others went as long as forty-one days.

In closing, I would just like to emphasize the two basic factors: In peptic esophagitis, we have a loss of a cardia sphincter mechanism and we have the great vulnerability of the esophageal mucosa. This means that either the sphincter mechanism has to be restored or else the mucosa of these two organs has to be separated. Then, too, it is important to differentiate between the two types of individuals, the person with a normal gastric secretion or the type with an ulcer diathesis, in order to select the proper operation.

EXPERIENCES WITH THE MANAGEMENT OF SEVERE BLEEDING FROM PEPTIC ULCER

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THE management of severe bleeding from the stomach and duodenum is still a subject of controversy. Opposite poles of opinion are represented by Andresen,[2] who prefers to treat all cases of bleeding ulcer by conservative measures, and by Stewart and associates,[13, 14] who recommend operation for all cases of severe bleeding.

In the past four years at the Roper Hospital, a middle ground has been chosen. Patients with severe hemorrhage are hospitalized under the joint care of an internist and surgeon. Blood is immediately drawn for typing, cross-matching, and determination of the hematocrit level. The bleeding, clotting, and prothrombin times are also determined. As soon as type specific blood is available, transfusions are started. The patient is given a modified Sippy regimen by mouth, including 60 c.c. of milk and cream every hour. An alkali is also given every hour and antispasmodics every four to six hours. Nasal oxygen is administered as long as shock is present. Blood pressure, pulse, and the condition of the skin are checked frequently, and until the rapidity of bleeding is determined, or until bleeding has apparently ceased, the volume of packed cells is determined every few hours. Evans blue dye determinations might be more accurate in studying blood volume loss, but we have not used them. Blood transfusions are continued until the peripheral circulatory status of the patient is stable and until the hematocrit reaches a level of about 30. After this, sufficient blood transfusions are given to maintain a stable circulatory status, and to maintain the hematocrit at a level above 30. During the first twenty-four hours, oral fluids are restricted to the quantities of fluid given in the diet and with the alkali, and supplementary fluids which may be necessary for hydration are given parenterally.

As far as diagnosis is concerned, if the patient has had a recent x-ray examination indicating the presence of a gastric, duodenal, or marginal ulcer, it is felt that no further radiologic investigation is indicated. However, we believe that it is desirable to establish a definite anatomic diagnosis in all patients with upper gastrointestinal hemorrhage as early as possible. Therefore, when the patient's circulatory status is stabilized, x-ray films are made as soon as possible by the Hampton technique, careful examination of the esophagus being made to rule out esophageal varices, and examination of the stomach and duodenum being carried out without palpation. In only one case was it suggested that bleeding was exacerbated by this radiologic maneuver. If it is thought desirable, the examination can be carried out while the patient is receiving blood transfusions. The accuracy of such studies is remarkably good but, in the best of hands, mistakes will be made, and in patients whose bleeding ceases, further radiologic investigation after an interval of ten to fourteen days with fluoroscopic palpation of the stomach and duodenum should be carried out before a diagnosis is accepted as final.

In general, it has been the policy to treat all patients in this conservative manner, the patient being followed by both the physician and surgeon, and only those patients who appear to have the "fatal type of hemorrhage," as

Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

described by Heuer,[7] are submitted to emergency operation. If the selection of these cases is made correctly, there should be no mortality from bleeding with conservative treatment and, if the selection is made promptly, the mortality rate for emergency surgery should be at acceptable levels. When possible, a decision for emergency surgery should be made in the first twenty-four to forty-eight hours after admission, although the "golden forty-eight hours" mentioned by Finsterer[5] has not been established as an ironclad rule.

The criteria for the choice of such patients for emergency operation have been repeatedly discussed in the literature, and the more important of these appear to be concerned with the age of the patient, the location of the ulcer, the size of the ulcer, the chronicity of the ulcer, and the initial response to conservative therapy. Certainly, most of the deaths from bleeding ulcer occur in older patients, and the tendency has therefore been to be more aggressive in operative attack on patients of advancing years with severe bleeding. Ulcers on the lesser curvature of the stomach, which erode the left or right gastric arteries or their branches, and ulcers on the posterior wall of the duodenum, which erode the gastroduodenal or superior pancreaticoduodenal arteries or their branches, are more likely to require emergency surgery, while ulcers in other locations are more likely to cease bleeding on conservative therapy. It has been said that the larger the ulcer and the longer it has been present, the greater is the likelihood that a dense fibrous base will be present which will prevent an eroded vessel from contracting or retracting, particularly if arteriosclerosis is also present, and such cases may thus require emergency surgery. Holman[9] has observed that patients who respond poorly to initial conservative therapy for bleeding will be likely to continue to respond poorly, and also that recurrence of bleeding in a patient who is hospitalized and on medical therapy is a grave prognostic sign. With these criteria in mind, decision for or against surgery is made, if possible, within the first twenty-four or forty-eight hours after admission. We have not been able to decide on any definite rule, like that of Dunphy and Hoerr,[4] but one of the chief points suggesting the necessity of operative intervention has been the lack of good or sustained improvement after a reasonable attempt at blood replacement. The other factors (age, type and location of the ulcer) also contribute to this decision, but in varying degree as part of the over-all evaluation.

Once surgery is decided upon, a Levin tube is passed into the stomach and the contents are emptied. Oral feedings and medications are stopped. The operation is carried out under general anesthesia and, at operation, the first efforts are made to locate the bleeding point, isolate it, and control the bleeding. After control of the bleeding, the improvement in the general condition of these patients is often dramatic and the surgical procedure from that point onward can be carried out in a relatively leisurely fashion. When no ulcer is palpable at operation, the operator is faced with a difficult decision, but in general, it has been our policy to carry out an empiric or "blind" gastric resection, provided that the operator is satisfied that the site of the bleeding is the stomach or duodenum, and provided that esophageal varices have been ruled out satisfactorily. We have not used gastrotomy or duodenotomy routinely to explore for the bleeding point, and in at least one case in the series here presented, this method was disappointing. However, if empiric gastric resection is decided upon, an open type of closure of the duodenal

stump is performed so that the duodenum remaining can be explored partially in an effort to demonstrate a bleeding point. If a definite ulcer is palpable, subtotal gastric resection is carried out in the same manner as is used for elective cases, removing approximately three-fourths of the stomach together with the ulcer, if possible, and performing a Hofmeister gastrojejunostomy. Although a short loop postcolic gastroenterostomy is preferable in cases of duodenal ulcer, the antecolic anastomosis is less time consuming and, consequently, if the patient is in relatively poor condition, as many of these patients are, the antecolic anastomosis is carried out. Dehiscence of the abdominal wound is so common in patients who have had severe bleeding that through-and-through wire stay sutures are routinely employed in the closure of the wound.

In a period of a little less than four years, between Oct. 1, 1949, and July 1, 1953, ninety-nine patients in the Roper Hospital were diagnosed as having bleeding peptic ulcer. These ninety-nine cases include only those with active bleeding while in the hospital. In many of these cases, bleeding was quite mild, and in an effort to avoid the confusion which exists with regard to the severity of hemorrhage in many publications on the subject, the cases have been arranged according to the classification of Hoerr, Dunphy, and Gray[8] (Table I). The ninety-nine admissions represent ninety-four patients, four patients having had two admissions for bleeding, and one patient having had three admissions for bleeding.

TABLE I. DEGREE OF HEMORRHAGE (CLASSIFICATION OF HOERR, DUNPHY, AND GRAY[8])

Group I:	"Moderate"
	Melena or hematemesis
	No syncope or hypotension in hospital
	Hematocrit above 30
Group II:	"Severe Compensated"
	Circulation stabilizes after admission to hospital
	May bleed for several days
	Hematocrit 30 or less
Group III.	"Severe Uncompensated"
	Marked shock on admission
	Bleed steadily for some time
	Hematocrit below 30
Group IV.	"Exsanguinating"
	Fail to maintain stable circulation despite transfusions of 500 c.c. every eight hours
	Fall in hematocrit despite transfusion
	Periodic episodes of syncope and hypotension

There were twenty-seven patients whose bleeding was classed as "moderate" (Group I). These cases were not of particular interest to the surgeon, and in most cases the patients required no transfusions. All of them were treated conservatively, and there were no deaths (Table II). One patient in this group later had an elective gastroenterostomy performed for a duodenal ulcer with pyloric obstruction and marked surrounding inflammatory reaction. It is interesting that he was subsequently admitted for hemorrhage from a marginal ulcer, which was likewise treated conservatively. Twenty-five patients had hemorrhage classified as "severe compensated" (Group II). Twenty-four of these were treated conservatively, and all survived. One patient in this group, who bled slowly for several days, was submitted to subtotal gastric

resection (for duodenal ulcer) while still bleeding because elective resection had been decided upon, and there appeared to be little or no reason for delaying the operation. Although this procedure was carried out while the ulcer was bleeding, it scarcely could be classified as an emergency procedure. This patient also survived. Three patients in Group II were later admitted to the hospital and elective subtotal gastric resections were carried out, in each instance for duodenal ulcer, and all of these survived elective operations.

TABLE II. BLEEDING ULCER

Group I	*27 Cases*
All treated conservatively, no deaths	
1 Elective gastroenterostomy for duodenal ulcer at later admission, subsequent hemorrhage from marginal ulcer	
Group II	*25 Cases*
24 Treated conservatively, no deaths	
1 Subtotal gastric resection for duodenal ulcer, survival	
3 Elective subtotal gastric resections for duodenal ulcer at later admissions, no deaths	

TABLE III. BLEEDING ULCER

Group III	*24 Cases*
23 Treated conservatively, no deaths	
1 Subtotal gastric resection, survival (duodenal ulcer with obstruction and hemorrhage)	
4 Delayed elective gastric resections, no deaths (one gastric ulcer; three duodenal ulcers)	
1 Delayed elective vagotomy and gastroenterostomy, death (gastric and duodenal ulcers)	
2 Elective gastric resections for duodenal ulcer at later admission, no deaths	

Twenty-four patients were classified as having "severe uncompensated bleeding" (Group III). Surgery was carried out for one of these patients during the bleeding phase, because there was associated pyloric obstruction, and recovery was satisfactory after subtotal gastric resection. The remaining twenty-three patients were treated conservatively, and all survived (Table III). Four of the patients treated conservatively remained in the hospital for later elective gastric resection; these included one patient with a lesser curvature gastric ulcer and three patients with duodenal ulcers. The result of surgery was satisfactory in each instance. One patient who had both a lesser curvature gastric ulcer and a posterior wall duodenal ulcer, and who had had three previous episodes of hemorrhage, after conservative treatment was submitted to elective operation; because of severe renal disease, vagotomy and gastroenterostomy were carried out in preference to gastric resection, but the patient succumbed following the operation. Two other patients in this group treated conservatively later returned to the hospital for elective gastric resection for duodenal ulcer, and the outcome of these operations was satisfactory.

The Group IV cases ("exsanguinating") are of particular interest (Table IV). There were twenty-three patients in this group, of whom twenty-one

were submitted to emergency operation, and only two were treated conservatively. One of the two patients treated conservatively died of recurrent hemorrhage. His history is given later. The second patient in this group treated conservatively is also reported here in detail; he later had an elective gastric resection for lesser curvature gastric ulcer with satisfactory recovery. Twenty-one patients in this group were submitted to emergency operation and four of these died, a mortality rate of 19.0 per cent. In eighteen cases the operation was subtotal gastric resection, and fifteen of these patients survived. In one case, the operation was simple excision of a gastric ulcer, in another exploratory gastrotomy alone, and in another excision of polyps in a case of previous subtotal gastric resection in which polypoid gastritis had developed in the gastric remnant. These cases are also reported later.

TABLE IV. BLEEDING ULCER

Group IV	*23 Cases*
2 Treated conservatively, 1 death	
21 Emergency operations, 4 deaths, mortality 19.0%	
18 Subtotal gastric resections, 3 deaths	
1 Excision of gastric ulcer, death	
1 Excision of polyps of gastric remnant, survival	
1 Exploratory gastrotomy, survival	
1 Delayed elective gastric resection for lesser curvature gastric ulcer, survival	

It is interesting that sixty-six of these admissions were on the private service, and although many of them were cases of mild hemorrhage, thirteen required emergency operation (Table V). There were no deaths in the entire group, whereas in the thirty-three service cases, there were a total of six deaths. This is no reflection on the resident staff, but probably is a result of (1) more experienced nursing care and a smaller patient-nurse ratio on the private side and (2) the poor nutritional state and high incidence of associated systemic disease in the service patients.

TABLE V. BLEEDING ULCER

		Mortality
Private cases (66)		
53 Treated conservatively		0
11 Gastric resections		0
1 Excision of gastric polyps		0
1 Exploratory gastrotomy		0
	66 Cases	No deaths
Service cases (33)		
23 Treated conservatively		1 (4.4%)
9 Gastric resections		3 (33.3%)
1 Excision of gastric ulcer		1 (100.0%)
	33 Cases	Deaths 5 (15.1%)
+ 1 Death after elective surgery		
		Deaths 6 (18.1%)

The results in the entire series are summarized in Table VI. In ninety-nine cases of bleeding, there were six deaths, a mortality rate of 6.1 per cent. Only five of these deaths were due to bleeding or to surgery at the time of

bleeding, the other death following elective surgery. The mortality rate in twenty gastric resections carried out in the bleeding phase was 15.0 per cent.

TABLE VI. BLEEDING ULCER, SUMMARY

		Deaths	*Mortality*
76	Treated conservatively	1	1.3%
20	Gastric resections while bleeding	3	15.0%
3	Other procedures while bleeding	1	33.3%
99	Bleeding cases treated	5	5.1%
	Death following later elective surgery	1	
99	Total hospital mortality	6	6.1%

CASE REPORTS

The deaths were as follows:

1. Mrs. J. R., a white woman, aged 71 years, who was admitted because of anemia, several days after admission developed profuse upper gastrointestinal hemorrhage accompanied by severe hematemesis. An upper gastrointestinal series made while she was bleeding was somewhat inconclusive, although there was suggestive evidence of duodenal ulceration. During the first twenty-four hours, the bleeding appeared to cease, and the circulatory status remained stable after 1 pint of blood was administered. However, the following day hematemesis recurred, and bleeding persisted despite the administration of 1,500 c.c. of blood. At this time she developed pulmonary edema, and for this reason operation was postponed. On the third day of bleeding, after the administration of a total of 7 pints of blood in the preceding seventy-two hours, emergency subtotal gastric resection was carried out, and at operation a large posterior wall duodenal ulcer was found, in the center of which was a large eroded vessel. The patient tolerated the procedure fairly well, and except for mild basal atelectasis and pneumonia in the right lower lobe, the postoperative course was satisfactory until the third postoperative day, when, while sitting up in a chair, she suddenly gasped for breath and expired. The clinical impression was that the cause of death was coronary occlusion or pulmonary embolus. Autopsy was obtained but did not reveal the exact cause of death.

Comment.—Although there was some delay in the institution of emergency surgical therapy because of the development of pulmonary edema and because of the equivocal x-ray findings, this death was probably not preventable. This is an illustration of the fact that patients who require emergency surgery are likely to be extremely poor operative risks.

2. M. L., a 65-year-old Negro man, was admitted for treatment of cardiac failure. Four days following admission, he was found to be passing tarry stools, and these persisted for the next two days despite daily transfusions. An upper gastrointestinal series revealed a large lesser curvature gastric ulcer. Cardiac failure was incompletely controlled, and dyspnea and, at times, Cheyne-Stokes respiration persisted, and his sensorium was quite cloudy. For this reason, operation was deferred, and efforts were made to maintain the blood volume with transfusions. Finally, although it was recognized that the chances of death were great whether or not operation was performed, under local anesthesia, the gastric ulcer, in the center of which was a large eroded branch of the left gastric artery, was excised, since it was felt that subtotal resection was utterly out of the question. He survived for twelve days after this operation, but became progressively more stuporous, developed consolidation in the lung bases, and a left hemiparesis, and died on the twelfth postoperative day. Autopsy was not obtained.

Comment.—Death appeared to be the only likely outcome whether or not operation was advised for this patient, but it was felt that removal of the

bleeding might give some opportunity for better control of the cardiac, renal, and cerebral status.

3. M. B., a 56-year-old Negro man, was admitted because of severe cardiac failure on the basis of arteriosclerotic and hypertensive disease. He was digitalized, and given diuretics, but the cardiac status was incompletely controlled when he began to pass tarry stools three days after admission. An upper gastrointestinal series was made and revealed the presence of a lesser curvature gastric ulcer. Electrocardiograms at this time showed evidence of a probable anterior myocardial infarction. He received one transfusion a day for the next four days, and at the end of that time all evidence of bleeding had ceased. However, he continued to complain of epigastric pain and, despite the administration of alkali and antispasmodics, he developed definite signs of perforation on the twentieth hospital day. When a Levin tube was passed into the stomach, a considerable amount of blood was evacuated. At operation, a small perforation in a large lesser curvature gastric ulcer was found, and the edge of the ulcer was bleeding moderately. Because of the cardiac status, it was felt that he would not tolerate gastric resection, and the perforation was closed with an omental graft after a biopsy of the ulcer was taken. Postoperatively he did fairly well for the first few days, and there was no further evidence of significant bleeding until six days after operation. At this time it was noted that the blood urea nitrogen had risen to 49. Again conservative treatment was attempted, but bleeding persisted, and consequently, fourteen days after the closure of the perforation, subtotal gastric resection was carried out. Postoperatively, the blood urea nitrogen continued to rise and his status progressively deteriorated. Finally, a duodenal fistula developed, and the patient died seven days after the operation.

Comment.—This patient presented a difficult problem because of bleeding and perforation in association with severe cardiorenal disease. It is possible that the result might have been more favorable, had subtotal gastric resection been performed at the time of the perforation.

4. A 42-year-old Negro woman, who had a typical ulcer history of three years' duration, was admitted three hours after having vomited a large amount of blood. She had had two previous episodes of hematemesis in the preceding three years. On admission, she was not in shock, and x-ray examinations revealed the presence of a large lesser curvature gastric ulcer. Blood transfusions were started, but unfortunately, the patient was given, through error, 150 c.c. of blood of the wrong type at the time of the second transfusion. By the time the error was discovered, massive hemoglobinuria had developed, and this was followed by marked oliguria. She continued to complain of pain, and the vomiting of blood persisted. Only by the constant administration of blood under pressure could the circulatory status be maintained. Consequently, despite almost complete anuria, emergency operation was decided upon, and a subtotal gastric resection was carried out. Postoperatively, there was oozing of blood from the gastric remnant, and also from the wound, and the extremely minute amount of urine which was passed was grossly bloody. She developed atelectasis in both lung bases, which improved somewhat following bronchoscopy. This was thought to be due to blood which had been vomited and aspirated before operation. Urine output continued to be extremely scanty, and although the pulmonary ventilation improved, she suddenly expired on the third postoperative day. At autopsy the presence of acute lower nephron nephrosis was confirmed, and capillary hemorrhages were also noted in the kidneys, pancreas, gastric remnant, peritoneal cavity, endocardium, and pleura.

Comment.—This death is the unfortunate result of a grievous human error in the administration of a blood transfusion. In the presence of extreme oliguria, the operative risk was magnified many times, but it was obvious that the patient would not survive massive bleeding much longer, and consequently,

the risk was accepted. Development of a generalized bleeding tendency following the administration of mismatched blood has been noted by Friesen and associates.[6]

5. B. N., a 57-year-old white man was admitted in deep shock about two hours after he had vomited a large amount of bright red blood. He gave a history compatible with that of peptic ulcer for the preceding two months. During the next five hours, he received 5 pints of blood, and only toward the completion of the fifth transfusion did the blood pressure stabilize at an apparently normal level of 140/80. The peripheral circulatory status then remained stabilized, and the hematocrit, which was 28 volumes per cent three hours after admission, was 34 volumes per cent six hours after admission, and 38 volumes per cent ten hours after admission. An upper gastrointestinal x-ray film was made and showed what appeared to be a large duodenal ulcer. It appeared that bleeding had ceased, and no further transfusions were given. Suddenly, about twelve hours after admission, and at least four hours after his return from the x-ray examination, the patient vomited approximately 2,000 c.c. of old blood, went into deep shock, and despite the administration of blood, promptly expired.

Comment.—It is possible, but doubtful, that the radiologic examination caused the recurrent hemorrhage. The response of this patient's circulatory status to initial blood transfusions was extremely poor, and he received 2,500 c.c. of blood before the circulation was stabilized. It is probable that this represents an error in surgical judgment, and that the patient should have been offered emergency surgery in the light of his poor initial response.

6. L. S., a 57-year-old Negro woman, had had ulcer symptoms for the preceding year, during which time she had been hospitalized on three occasions for moderate upper gastrointestinal bleeding. In addition, she had marked hypertension (200/120) and evidence of chronic nephritis with the urine showing 3+ albumin, as well as a few red cells and casts, and a blood urea nitrogen of 36. Maximum concentration was 1.013. The bleeding subsided with conservative antiulcer therapy, and the anemia was corrected with transfusions. Because of four episodes of hemorrhage, it was felt that operation was indicated, but because of the extremely poor renal status, gastrojejunostomy and vagotomy were chosen as a lesser procedure. This operation was carried out twenty-five days after admission. Postoperatively, the blood urea nitrogen began to climb rapidly, and despite the administration of large amounts of fluid, she expired on the sixth postoperative day.

Comment.—This patient survived the bleeding episode, but it was thought that with pronounced arteriosclerosis and hypertension, the next bleeding episode might be fatal. Consequently, operative therapy was felt to be indicated. In retrospect, it was unwise to advise this in the face of severe renal damage.

The following cases are of sufficient special interest to record some of the details of their course:

1. A. C., a 55-year-old white man, was admitted to the hospital in mild shock with a history of having passed tarry stools and vomited coffee-ground material in the twenty-four hours preceding admission. He had a vague history of indigestion, but not a typical ulcer history. Peripheral circulatory status was restored to normal after he had received 1,000 c.c. of blood. A barium swallow was then given, and the x-ray films were reported as showing "a smoothly marginated polypoid filling defect of the fundus of the stomach which probably represents a mucosal polyp." It was the clinical impression that this might be a leiomyoma with ulceration. Moderate bleeding continued despite the ad-

ministration of a total of 3,500 c.c. of blood, and emergency operation was decided upon. At operation, no tumor or ulcer was palpable, but the stomach was filled with blood clots. The stomach was opened widely, and the blood evacuated, and it then became apparent that the previously noted filling defect was simply adherent blood clot. No ulcer or erosion could be visualized in the stomach or first portion of the duodenum. The wound in the stomach was therefore closed, and the abdomen closed. Bleeding continued after operation, blood passing through the Levin tube until the tube was removed. During the next ten days the patient received a total of 10,000 c.c. of blood, and despite an antiulcer regimen, bleeding continued until the tenth postoperative day, at which time it ceased. During this time, the patient had developed bilateral basal atelectasis, and partial dehiscence of the wound with superimposed wound infection. These difficulties were corrected by appropriate therapy. A complete work-up after the bleeding had ceased failed to reveal any evidence of the source of bleeding, although there was a slight deformity of the duodenal bulb on radiologic examination. A complete hematologic work-up was within normal limits.

Comment.—The final impression was that this patient bled from a gastric or duodenal erosion. This alarming experience convinced us of the value of empiric gastric resection in operations for severe bleeding from the stomach and duodenum.

2. A. L., an 80-year-old white man, was admitted with a history of hematemesis and the passage of tarry stools of sixteen hours' duration. He had had symptoms suggestive of a peptic ulcer for the preceding three years, and shortly after the onset of these symptoms, a gastrointestinal series had been performed elsewhere, and had been reported as showing a duodenal ulcer. After hospitalization, he was given one transfusion of 500 c.c. of blood, and showed no further evidence of shock until the following day, at which time he again began to vomit blood and pass tarry stools. At this time he had a marked tachycardia, moist skin, and cyanosis which was thought to be on the basis of pulmonary emphysema and marked diminution of the blood volume. During the next forty-eight hours, he received 5 pints of blood, and finally the circulatory status stabilized, bleeding ceased, and the hematocrit was stabilized at a level of 33 volumes per cent. A gastrointestinal series two days later showed a large lesser curvature gastric ulcer. A medical antiulcer regimen was begun, and he remained in the hospital for the next three weeks, at which time a repeat x-ray examination showed no evidence of healing of the ulcer. An elective gastric resection was then carried out, from which the patient recovered satisfactorily. The ulcer was reported as benign on microscopic examination. Just before the patient's discharge, a malignant polyp was removed from the rectum.

Comment.—According to the usual criteria, with the recurrence of bleeding, this patient should have been selected for emergency operation. However, because of the extremely poor pulmonary ventilation, with cyanosis at the time he developed shock, it was felt that he would not tolerate any operative procedure, and efforts at conservative therapy were continued with cessation of the bleeding. He tolerated elective operation surprisingly well.

3. I. R., a 38-year-old white man, for whom a subtotal gastric resection for duodenal ulcer had been performed elsewhere six years previously, was admitted because of mild bleeding, with the passage of tarry stools, and treated conservatively with cessation of the bleeding. A gastrointestinal series at this time showed hypertrophic rugae of the gastric remnant, but no evidence of marginal ulcer. Six weeks later he was admitted because of mild melena. Despite conservative antiulcer therapy, and the administration of thirteen transfusions of 500 c.c. each during the next week, this bleeding became progressively more severe. During the next ten days he received another 7 pints of blood, and at

the end of that time, the red cell count was 2.73 million, hemoglobin 8.0 Gm., and hematocrit 22 volumes per cent. At that time he went into moderate shock, and emergency operation was carried out. No ulcer was located, but when the gastric remnant was opened, three large sessile polypoid structures were noted which were oozing blood. These were removed and the mucosal defects closed. His postoperative recovery was entirely satisfactory, and he was discharged on the tenth postoperative day. One year later, he returned with moderate bleeding, which was treated satisfactorily by conservative means. An x-ray film at this time again showed hypertrophic rugae, but no evidence of ulceration.

Comment.—Perhaps it is not proper to include this case in a group of bleeding ulcers, but this is an extremely interesting late complication (bleeding polypoid gastritis), following subtotal gastric resection for bleeding duodenal ulcer.

DISCUSSION

Although the value of blood transfusions in the therapy of bleeding peptic ulcer is only occasionally[2] disputed at the present time, one still hears the argument that if too many blood transfusions are given, clotting cannot occur, or a clot in a vessel will be "blown out." There appear to be few clinical data to support such a conclusion, and recent experimental work[11] seems to indicate that a bleeding vessel will be plugged by clot more quickly if blood transfusions are administered. In any case, it is felt that blood transfusions are the most important element in the conservative treatment of bleeding ulcer.[10] A Sippy or similar-type feeding regimen seems to be valuable, whether because of a partial correction of hypoproteinemia, a diminution of hunger contractions of the stomach, or simply the providing of a substance for the acid-peptic mixture in the gastric juice to digest other than the clot at the ulcer site. Alkali is an important part of the feeding program.

The race and sex incidence in these cases is recorded in Fig. 1. This appears to show a relative increase in the number of Negro patients in Groups III and IV. This proportionate increase is probably more apparent than real since, because of limited bed space, the Negro service patient finds it difficult to enter the hospital until bleeding is rather severe. Amendola[1] has stressed the importance of hematemesis, and particularly the vomiting of bright red blood, as a grave prognostic sign. Fig. 2 indicates that although hematemesis was a little more common in cases of exsanguinating bleeding, a high percentage of patients in each group had vomited blood, and therefore it appears to be of no particular prognostic significance. For years, it has been repeatedly stressed that bleeding from peptic ulcer is much more serious in the older age group. It was surprising to find that in this series, although the average age of the patients increased with the seriousness of the bleeding (Fig. 3), the difference was not striking, and several superannuated individuals in Groups I, II, and III were treated satisfactorily by conservative measures. The relationship of age to mortality probably depends on the greater likelihood of the presence of arteriosclerosis in the older age group, as well as an increased susceptibility to superimposed infection and the presence of other associated systemic disease. Fig. 4 illustrates the duration of previous ulcer symptoms in this series of cases. While no conclusions can be drawn, it is apparent that

bleeding is often more serious in patients with a short ulcer history than in those with a long ulcer history. This is particularly apparent as related to cases of gastric ulcer (Fig. 5).

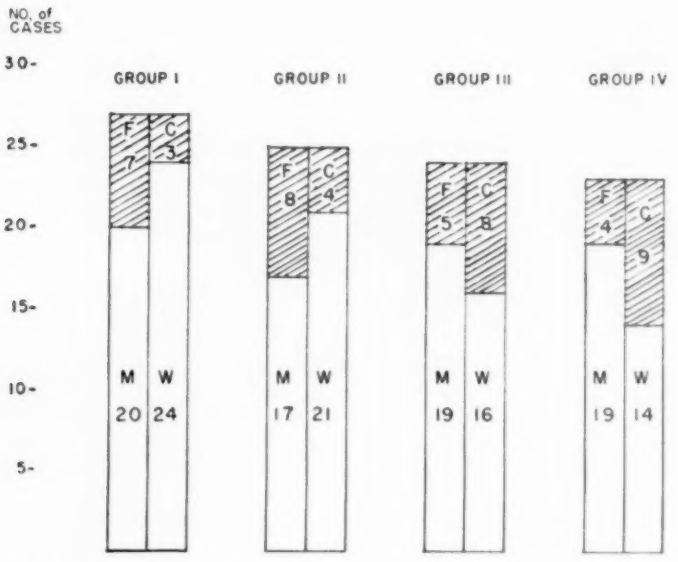

Fig. 1.—Incidence of sex and race in bleeding ulcer cases.

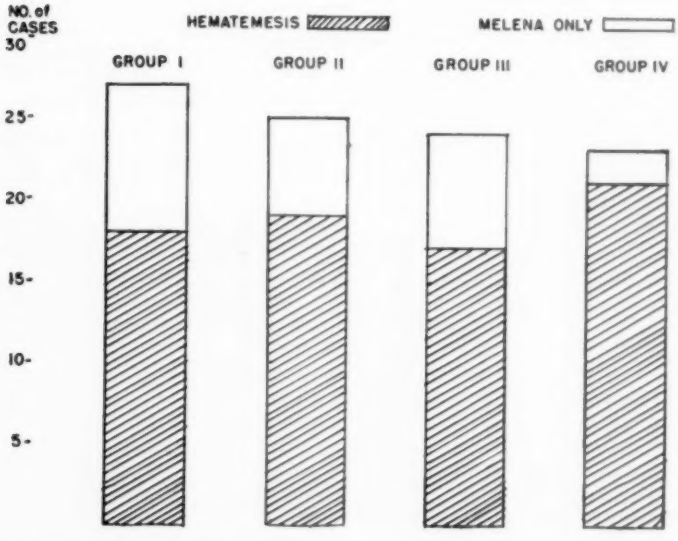

Fig. 2.—Incidence of hematemesis in patients with bleeding ulcer.

It has been noted in many previous articles on the subject that exsanguinating hemorrhage is more likely to arise from gastric ulcer situated on the lesser curvature or from duodenal ulcer eroding the posterior wall of the duodenum. This has been confirmed by the operative findings in most of these cases of exsanguinating hemorrhage. The grave prognostic significance of

gastric ulcer with severe hemorrhage has been previously emphasized by Sandusky and Mayo,[12] and this is borne out in Fig. 6. In a total series of seventeen gastric ulcers with bleeding, in five cases the bleeding was classified

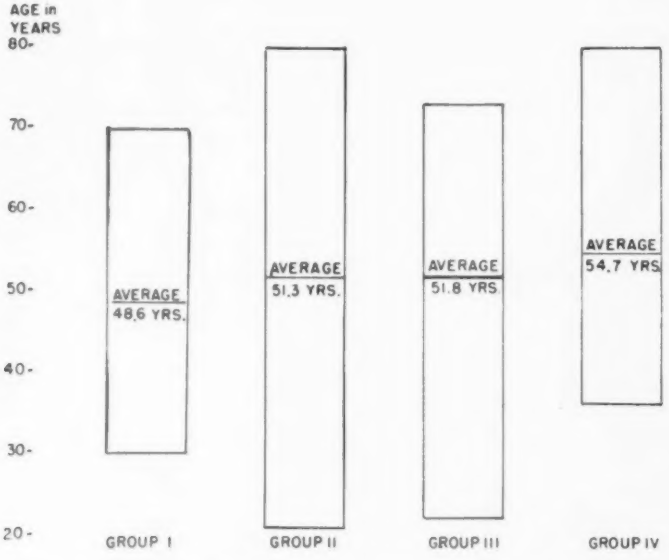

Fig. 3.—Age distribution in patients with bleeding ulcer.

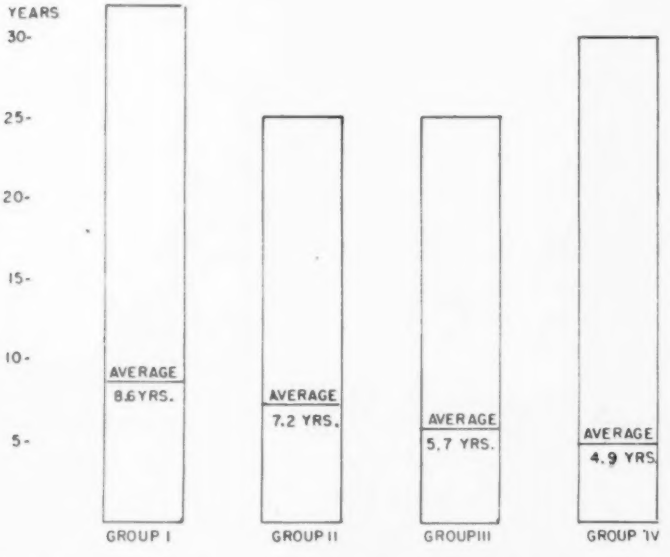

Fig. 4.—Duration of previous ulcer symptoms in bleeding cases.

as being of the severe uncompensated type and in seven cases as exsanguinating. It is perhaps purely coincidental that gastric ulcers were present in four of the six cases in which death occurred.

Empiric or (blind) gastric resection was carried out in four patients in the series, in whom it was demonstrated that bleeding was coming from the

stomach and duodenum, and who had no evidence of esophageal varices. In three of these cases, there was radiologic evidence of a duodenal ulcer, and in the other case, of a patient with a previous gastroenterostomy, there was prior radiologic evidence of a marginal ulcer, but these findings were not confirmed

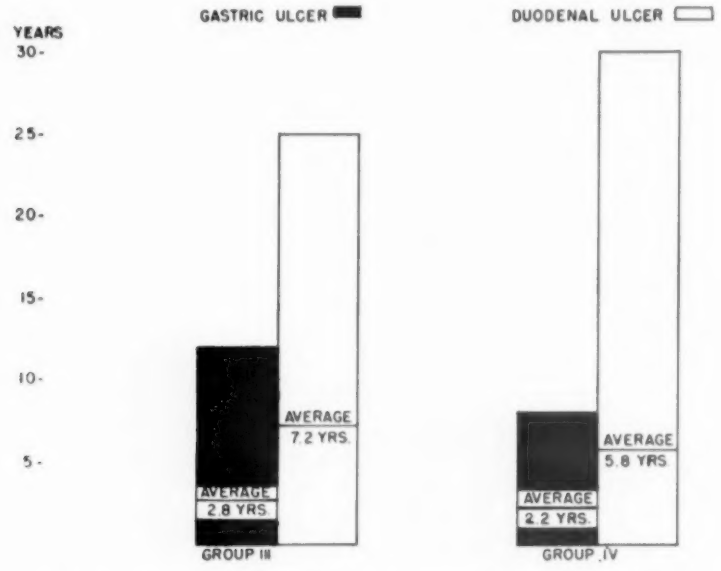

Fig. 5.—Duration of symptoms in cases of severe bleeding.

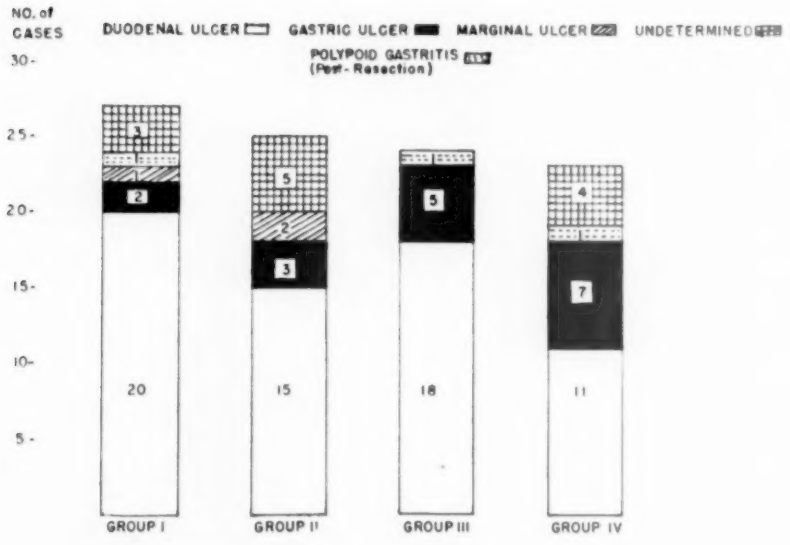

Fig. 6.—Site of bleeding.

at exploration or when the resected material was examined in the pathology laboratory. Yet, in each instance, bleeding promptly ceased following gastric resection. One of these patients has been followed two years, one one year, and one six months, and in each case the result has been entirely satisfactory

without evidence of recurrent bleeding. The fourth patient has been lost to follow-up. In view of a distressing experience in the one case reported in which exploratory gastrotomy was carried out and definitive operative therapy avoided when no lesion could be located, these results seemed to support the contention of Cooper and Ferguson[3] and Thieme[15] that empiric gastric resection may be valuable in selected cases. Heuer[7] has noted that in one instance of gastric bleeding, the causative erosion could not be found by the pathologist at autopsy until a stream of fluid forced through the left gastric artery demonstrated the site of bleeding.

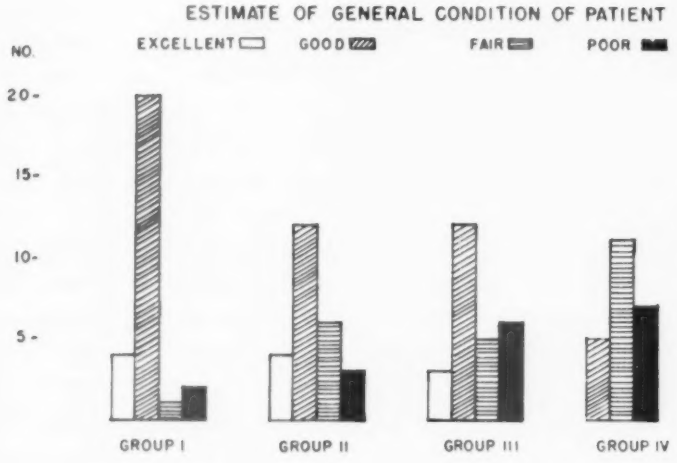

Fig. 7.—Estimate of general condition of patient.

The sensibilities of the conservative surgeon are offended when it appears necessary to choose the poor operative risks for an operative procedure, and to avoid operating on those who are excellent risks, and yet this is exactly what must be done in the individualized management of severe bleeding from peptic ulcer. Unfortunately, as Fig. 7 illustrates, the patients in whom the most serious bleeding occurs will inevitably be the poorer operative risks, not only because of the bleeding itself, but because of associated systemic disease. If the better operative risks are selected for surgery, the surgical mortality rate will be diminished, but the mortality rate from medical therapy will be greatly increased, as will the over-all mortality rate. If patients are properly selected for operation, there should be little or no mortality from bleeding treated conservatively. When such methods of selection are employed, medical and surgical mortality rates obviously are not comparable.

Perhaps the most significant prognostic factor in the experience reported here, as in the experience previously reported by Holman,[9] is that patients who respond promptly to initial blood transfusions usually do well on conservative therapy, but those who respond poorly to initial transfusions, or who have a recurrence of bleeding while on a conservative regimen, will do poorly if medical therapy is continued. As far as elective operation because of a history of bleeding is concerned, it has been the policy to advise elective operation

in cases of duodenal ulcer for those under the age of 40 years who have had two or more episodes of fairly severe hemorrhage, and to advise elective operation for those over 40 years who have had a single severe episode of hemorrhage from which they have recovered. Severe hemorrhage from gastric ulcer in any patient should be an indication for elective resection. On this basis, elective resections have been performed in ten cases without a death, and one elective gastroenterostomy was also carried out. However, the patient subjected to elective vagotomy and gastroenterostomy died of renal failure.

SUMMARY

A series of ninety-nine cases of bleeding on the basis of peptic ulcer has been presented. Of these, forty-seven patients were classified as having severe hemorrhage. There was one death in seventy-six cases treated conservatively, and four deaths in twenty-three patients treated by operative measures. One other patient failed to survive elective surgery performed after cessation of the bleeding. A mode of combined medical and surgical therapy is presented, emphasis being placed on the importance of giving adequate blood transfusions in the treatment of bleeding ulcer, individualization of cases in choosing those which will require emergency gastric resection, and the serious prognostic significance of (1) gastric ulcer associated with severe hemorrhage and (2) poor initial response to transfusions or recurrence of bleeding after the institution of medical therapy. Patients with severe hemorrhage from gastric ulcer and those who show a poor or unsustained response to adequate transfusions early in the course of management, and those who bleed again after cessation of hemorrhage, have been observed in our experience to have a poor prognosis, and should be selected for emergency gastric resection. When esophageal varices have been ruled out, and it has been determined that the hemorrhage is arising from the stomach or duodenum, even if an ulcer cannot be demonstrated at laparotomy, we believe empiric gastric resection should be performed. Illustrative cases have been presented.

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DISCUSSION

DR. JOHN D. STEWART (Buffalo, N. Y.).—Dr. Mayo asked me if I would say a word on this subject. I think he thought that I would disagree with him. I am afraid I am going to have to disappoint him.

The areas of difference of opinion are in regard to details rather than principles, in my opinion. The patients with dangerously bleeding peptic ulcers can be treated in three ways. They can be treated by operating on none of them, by operating on all of them, or by a combination of supportive and surgical measures, which implies a selection of cases to be treated surgically. It is with regard to the yardsticks by which we select cases that there is still disagreement.

I think it is fair to say that in this country most of us follow the third policy; namely, we believe in using a combination of supportive treatment plus operation where we think operation is likely to offer the patient the best chance of survival.

The criteria which we have used over a seven-year period have been associated with the treatment by blood replacement and gastrectomy in an urgent phase of 138 patients. During the same period, a somewhat larger number have been treated without operation for categorical reasons. The criteria that we have used have depended on the acuteness and the severity of the hemorrhage. After all, hemorrhage is what is endangering life, and the acuteness or the rapidity of the hemorrhage, we would all admit, is an important factor in determining the danger to the patient.

The method which Dr. Mayo has used, although differing in details from our plan, seems reasonable to me. His plan involves a somewhat indirect estimate of the gravity of the situation as compared with somewhat more direct evidence as obtained by blood volume measurement, repeated if need be.

If I may be permitted to speak of our own results instead of discussing Dr. Mayo's, we find that blood replacement and subtotal gastric resection in patients who have duodenal ulcer carry a mortality risk of approximately 6 per cent, but in cases of exsanguinating gastric ulcer, a somewhat higher mortality rate, approximately 10 per cent, prevails. These patients are patients whose circulating red cell mass has been bled down to 60 per cent or less. As a matter of fact, the average figures are around 40 per cent. The ones who were less severely bled out, as I said, have not been operated on in the acute phase of hemorrhage.

One of the interesting features that Dr. Mayo referred to, and I am sure he would like to say more about it if he had the time, is the variation in hospital population as it influences this problem. Everybody knows that the patients in the status of private patients, who take better care of themselves, and who have perhaps a lower incidence of associated disease, can be treated with more success with almost any method you use than the patient who comes in neglected and with various other untreated ailments. I am sure this point accounts for some of the discrepancies in the reported experience with this problem.

With regard to diagnosis, in closing, I would like to ask Dr. Mayo what in his experience has been the evidence of acute ulceration, which cannot be detected by external

examination of the stomach at the operating table. In our series of cases these comprise approximately 20 per cent of the total. They are just as dangerous as the penetrating ulcers, and may bleed just as severely. They are much more difficult to recognize either by x-ray studies or at the operating table, and it is possible that they represent an entirely different sort of disease from the ulceration seen in the chronic ulcer diathesis.

DR. STANLEY O. HOERR (Cleveland, Ohio).—I think that a 5 per cent mortality in the group of patients having urgent or emergency surgery for massive hemorrhage is a very enviable one. Furthermore, the fact that only one died in the medically treated group attests to the fact that many poor-risk patients must have been accepted for operation in Dr. Mayo's series.

I should like to comment briefly on extending diagnosis in the patient who comes to surgery without an accurately located bleeding point. In spite of emergency barium x-ray films, sometimes it is impossible to be certain just where the bleeding is coming from. After the decision has been made to operate as an emergency upon a patient who has not had the lesion satisfactorily demonstrated, we have found it useful to carry out esophagoscopy with the patient under general anesthesia. If the bleeding should be coming from unsuspected esophageal varices, a thoracotomy can be performed at once with transesophageal ligation of the varices. If the bleeding is not coming from esophageal varices, a laparotomy is carried out. If the bleeding point is not obvious with the abdomen open, we have found it useful to open the stomach and use a sterile sigmoidoscope to inspect the inside of the stomach. At the very least, this will determine whether the bleeding is actually coming from within the stomach, and at best the lesion will be seen. I have not been able to bring myself to perform a blind gastrectomy unless blood could actually be seen in the stomach on such a patient. If there is blood in the stomach and the bleeding point cannot be located either by external or internal inspection, a blind gastrectomy is fully justified because the resected stomach may contain the pathology. If the pathology lies above the resected stomach, resecting the stomach may cure it, although every effort must be made to be sure the bleeding is not coming from a high lesser curvature ulcer which should be resected.

DR. RALPH F. BOWERS (Memphis, Tenn.).—Thank you very much, Dr. Widger. Dr. Mayo invited me to discuss his paper for the same reason stated by Dr. Stewart. He thought our viewpoints would differ, and let me say that I think Dr. Mayo is a real peacemaker. It seems to me that he has done what inevitably happens in these controversies where a radical approach has been used by one group and a less radical approach by others—he has adopted the middle road and will consequently have many friends around the country.

In a more serious vein, I would like to say that the controversy has not reached a stalemate, but that more good than harm has been accomplished. Regardless of what Dr. Stewart may think or Dr. Mayo or Dr. Dunphy, Dr. Hoerr, the others, and myself may think, there has been a betterment of mortality rates in everybody's hands. For instance, Dr. Stewart has made us work awfully hard to give the best possible care to these patients, and I like to think that we have stimulated him to do something of the same nature.

Let me call your attention to this. There has been some melting of viewpoints as I see it. Most workers now agree that the obstructed bleeder, the bleeder who resumes bleeding on good medical care after cessation of the hemorrhage originally, the bleeder who cannot be controlled by medical measures after a reasonable attempt—these patients must receive gastric resection during the phase of active bleeding. So there is some melting of thought and action and a distinct betterment of the mortality rates.

Now, Dr. Mayo's 6 per cent mortality rate is a decent one. Uniformity of reporting has been lacking. It appears to be the cause of trouble. One method would include the fate of every bleeding ulcer in a given hospital, whether it is treated on the medical or surgical service. But we have not been as good as Dr. Stewart in the classification of the massive hemorrhage. Dr. Mayo includes all cases.

The number of patients who will need emergency gastric resection will be proportional to how good or how bad the medical therapy has been carried out. Good medical treatment will require less emergency operations, but cannot eradicate emergency procedures in all cases.

I hesitate to interpolate our results here, but if Dr. Mayo will permit me, I will mention the results for the 1953 cases, which have recently been compiled. As you know, we use a more conservative approach than some others.

We have treated seventy-one bleeding episodes during the past year. Four patients underwent emergency gastric resection during the period of active bleeding; we lost one, a 78-year-old man who had bled for seven days, not because of medical procrastination, but because the patient refused operation at the forty-hour level of observation. Obviously, death was imminent if medical therapy would be continued. Humanitarianism still demands that we attempt to save a patient's life, so the hazardous and futile operative procedure was performed. Thirteen, however, were operated on during the interval stage, a total of seventeen patients, which approaches Dr. Mayo's twenty-three operated cases. If our present pace continues, by the time we get to ninety-nine cases, we will operate on about the same number of patients. The difference will probably be that we will operate more in the safer interval stage. No patients were lost from medical therapy alone in these seventy-one cases. Consequently, we can see no reason to change our approach to the problem.

I wish to reiterate, however, that the Southern bleeding ulcer patient will respond to good medical therapy better than his Northern brother. Perhaps the emotional stresses and strains are less in the South at the present time.

DR. J. ENGELBERT DUNPHY (Boston, Mass.).—I would like to make one comment. This should be the comment to end all comments on this subject, but I am afraid it will not be. The reason there has been so much controversy is that if we did not have a controversy, we could not have written on the topic. I think the classic example of that is Dr. Bowers' presentation before—I think it was the American Surgical Association—where he said: "We don't agree with people who want to operate on these patients as an emergency." Among the references listed were Dunphy and Hoerr, so I pricked up my ears and expected something new. I read his paper, and he said exactly what we had said two or three years before, so that all we need to do now is understand each other a little better. I think we are all doing exactly the same thing, namely, operating only on those patients who would die if we did not operate on them. The real advance, I think, has been selling the "medical men" that you can work jointly on these cases with them and that it is a joint venture. The same approach is badly needed in some other fields of medicine and surgery; a classic example today in which this kind of cooperation is going to be needed to prevent controversy is the current question of when patients should undergo cardiac surgery.

DR. EDWARD L. HOWES (New York, N. Y.).—I would like to make comments upon two technical aspects of dealing with severe gastric hemorrhage. First, when the individual goes into the operating room, somebody other than the surgeon should take care of the bleeding problem. When Dr. Porter started with the use of the arterial transfusion in this type of case, we discovered after having it available for the treatment of several bleeding ulcers, that we had not used it. The venous pressure of the patient was a total guide to management of the transfusions at the operating table, and forcing the intravenous route was usually adequate. With somebody extra in the operating room taking venous pressures and giving the blood, the surgeon can concentrate on his problems and proceed in a relaxed and leisurely manner.

The second point is this: If the gastrectomy is to be performed, should the bleeding ulcer of the duodenum be left behind to bleed again? The best policy is to remove it or

at least to leave only its bed in the pancreas. Technically the procedure is simplified by mobilizing the duodenum through its descending portion, and then the ulcerated area can be approached from above and below.

DR. MAYO (Closing).—I wish to thank all of the discussants for their kind comments, and I appreciate Dr. Bowers' assigning me the role of peacemaker.

Dr. Stewart made an excellent point in connection with blood volume studies. We have not used the Evans blue dye determinations, but do plan to do so, and believe that they will prove to be more accurate than the hematocrit levels presently employed.

Both Dr. Stewart and Dr. Hoerr mentioned a problem which is a serious one, concerned with the patient in whom at operation one is unable to palpate any ulcer. There are those who feel that a wide gastrotomy is helpful, but as a result of our experience with one individual in whom this was carried out without finding the bleeding point, and who continued to bleed postoperatively, we do not feel that this will be valuable. Our present policy is to perform an empiric or blind gastric resection as long as we are sure that the patient does not have esophageal varices, and as long as we are satisfied that the bleeding is coming from either the stomach or duodenum. There were four such cases in the group of twenty gastric resections reported.

THE FATE OF HETEROLOGOUS ARTERIAL GRAFTS: AN EXPERIMENTAL STUDY*

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THE standards for procurement of arterial homografts for human use are necessarily rigid. Only individuals who died from causes other than malignant or infectious disease and in whom no arteriosclerosis is demonstrable are suitable donors. Furthermore, the body must be refrigerated, and the vessels should be removed within twenty-four hours of death. Accidental deaths so far have provided most of the human homografts used. The increasing utilization of vascular transplants has resulted in a need for arterial homografts that far exceeds the supply. Animals slaughtered for human consumption represent a readily available and practically unlimited source of arterial grafts. This study was undertaken to determine the feasibility of using heterologous arteries as vascular transplants.

Heterologous arteries were utilized experimentally as vascular transplant one-half century ago. The earliest attempts by Hopfner[9] with fresh grafts were unsuccessful. Subsequently, a number of investigators[1-3, 7, 8, 16-18] succeeded in transplanting fresh arterial heterografts. Similarly, heterografts preserved by refrigeration in physiologic saline solution and by formalin fixation were successfully employed. The most notable experiment was that of Carrel,[3] who transplanted a refrigerated segment of human popliteal artery into the abdominal aorta of a dog. Microscopic study more than four years later revealed the wall to be composed entirely of connective tissue with hyaline change and absence of muscle cells and elastic fibers. Carrel considered the graft functionally satisfactory. With the decline of interest in vascular transplants following World War I, the problem of arterial heterografts received little attention until recently, when a number of experimental[5, 6, 11, 12, 15] and clinical[10, 13] studies were made.

METHODS

Arteries obtained at the abattoir from freshly slaughtered hogs, sheep, and calves were placed immediately in physiologic saline solution. No attempt was made to remove the vessels under sterile conditions. In the laboratory, the vessels were washed several times in physiologic saline solution containing penicillin and streptomycin and were then cut into segments about 3 cm. long.

Early in the study, it became apparent that the thicker walls of vessels of sheep and calves rendered them less satisfactory for transplantation to the dog than those from hogs. Therefore, with the exception of one sheep artery and three calf arteries, all transplants were from hogs.

Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

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Two methods of preservation were employed to render the grafts nonviable: (1) fixation with 4 per cent neutral formalin and (2) freeze-drying. These methods were selected in the belief that devitalized heterologous tissue would produce less undesirable reaction in the host than viable tissue.

The formalin-preserved vessels, splinted with a glass rod to prevent curling, were placed in individual glass bottles filled with formalin, tightly stoppered, and stored at room temperature. About twelve hours prior to operation, they were washed several times and stored in the refrigerator in physiologic saline solution until used. The freeze-dried vessels were vacuum sealed in glass tubes and kept at room temperature. Approximately one hour before operation they were reconstituted in physiologic saline solution containing 500,000 units of penicillin and 0.5 Gm. of streptomycin per 500 ml. Just prior to implantation, loose adipose and areolar tissues were removed from the graft to be implanted, and the branches were ligated with 00000 arterial silk.

Carotid arteries and thoracic and abdominal aortas of dogs were used as recipient vessels. Anesthesia was induced by intravenous pentobarbital sodium. When thoracic aortic grafts were being transplanted, positive pressure respiration was achieved by endotracheal tube and mechanical respirator. The carotid artery was approached through a longitudinal incision in the neck, the descending thoracic aorta through an incision in the left fifth intercostal space, and the abdominal aorta through a midline abdominal incision. Segments 1 to 1.5 cm. long were removed from the host vessel between noncrushing clamps, and the defect was bridged by the heterologous graft. Anastomosis was accomplished with a simple continuous suture of 00000 arterial silk interrupted in two places. After the thoracic and abdominal aortic anastomoses were completed, the mediastinal pleura in the former and the posterior peritoneal layer in the latter were closed over the graft. Postoperatively, each dog received 300,000 units of penicillin daily for five to seven days.

TABLE I. HETEROLOGOUS ARTERIAL GRAFTS: CAUSES OF DEATH IN ANIMALS SURVIVING LESS THAN ONE MONTH

	GROUP I	GROUP II
Graft failure	4	2
Anesthetic	3	1
Respiratory infection	4	
Wound infection	3	
Other causes	4	1
Total	18	4

TABLE II. HETEROLOGOUS ARTERIAL GRAFTS: FATE OF ANIMALS SURVIVING MORE THAN ONE MONTH

	DIED	SACRIFICED	LIVING
Group I	5	20	1
	7-29 mo.	5-26 mo.	31 mo.
Group II	1	5	2
	13 mo.	18-20 mo.	20-21 mo.

TABLE III. HETEROLOGOUS ARTERIAL GRAFTS: CONDITION OF GRAFTS DEMONSTRATED BY AORTOGRAPHY OR AT NECROPSY

			PATENT		OCCLUDED	
	HOST VESSEL	NO.	NON-DILATED	DILATED	THROMBOSIS	CONSTRICTION
Group I	Carotid arteries	13				13
	Thoracic aorta	2	1	1		
	Abdominal aorta	11	5*	4		2
Group II	Abdominal aorta	8	3*	4*	1	

*One animal living.

Group I consisted of 44 dogs that received formalin-fixed grafts, and Group II consisted of 12 dogs that received freeze-dried grafts. Arteriographic studies were made on the surviving animals twelve to thirty months postoperatively. Except for 3 dogs kept for long-term observation, all were sacrificed. At necropsy, grafts were removed in continuity with adjacent host vessels and placed in 10 per cent formalin. Cross sections were taken from the center of the graft and longitudinal sections from the proximal and distal anastomoses for microscopic study. Paraffin preparations were stained with hematoxylin and eosin, van Gieson's stain, Weigert's elastic tissue stain, and Masson's trichrome stain.

Fig. 1.—Aortogram of aneurysm in a freeze-dried graft at thirteen months.

RESULTS

The formalin-fixed heterologous grafts (Group I) were implanted into the following vessels: carotid arteries, 14; thoracic aorta, 8; abdominal aorta, 22. Of the 44 dogs, 18 survived less than one month, graft failure accounting for 4 of these deaths (Table I). Of the remaining 26 animals, 5 died seven to twenty-nine months after operation from causes unrelated to the graft, 20 were sacrificed, and 1 is living thirty-one months postoperatively (Table II).

Of the 12 dogs receiving freeze-dried heterologous grafts (Group II) implanted into the abdominal aorta, 4 survived less than one month, with graft failure responsible in 2 (Table I); 1 died thirteen months postoperatively from

rupture of an aneurysm in the graft (Fig. 1) soon after retrograde aortography; 5 were sacrificed; and 2 are alive twenty and twenty-one months after operation, respectively (Table II).

In the dogs surviving more than one month, the condition of the grafts was determined by arteriography or at necropsy (Table III). Of the 26 grafts in Group I, 11 were patent and 15 were occluded. Five of the patent grafts were dilated. Of 8 grafts in Group II, 7 were patent and 1 was occluded by a thrombus. Four of the patent grafts were dilated.

A.

B.

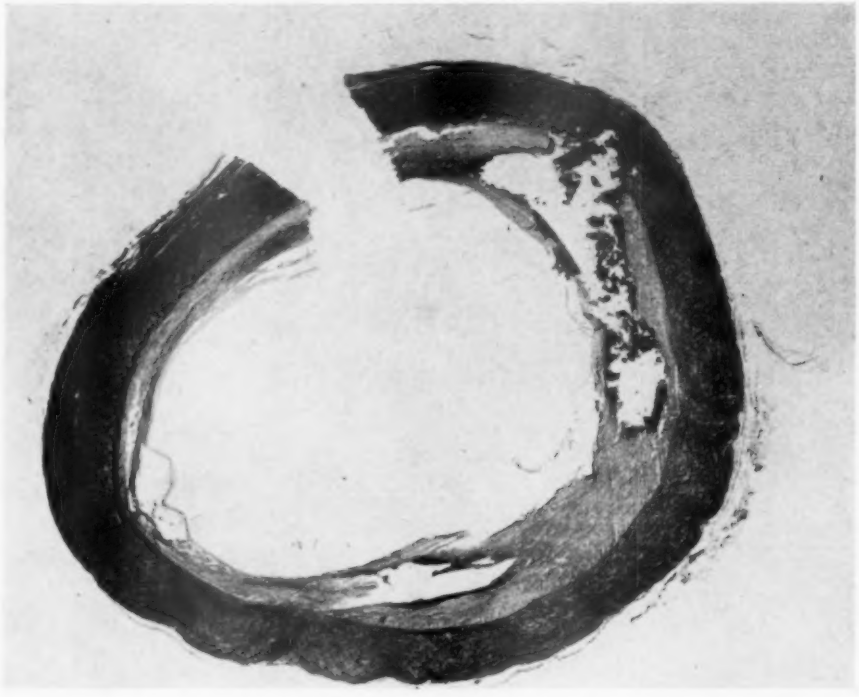
Fig. 2.—*A*, Patent, nondilated, formalin-fixed graft twenty-six months after transplantation.

B, Same specimen opened longitudinally revealing smooth intimal surface.

Morphologic Studies.—Of 15 formalin-fixed grafts (Group I) removed for examination from animals dying one to ten days after operation, 3 had gross evidence of necrosis and infection; the anastomoses were disrupted in 1 graft. The transplants of the remaining 11 animals which died from unrelated causes were patent in 7 and thrombosed in 4 instances.

Grafts were studied histologically three, six, and seven days after transplantation. The intima was absent over most of the inner surface, the inner

layer of the graft being made up of elastic fibers of the media. In some places a thin fibrin deposit had replaced the intima. The trough at the anastomosis, formed by eversion of the ends of the graft and host vessel, was filled with a wedge-shaped thrombus which extended onto the graft for varying distances. This thrombus was continuous with that surrounding the sutures. There was nuclear staining in the media with perfect preservation of structure and pattern of the elastic fibers. Collections of erythrocytes were observed between the elastic fibers. In the adventitia there were granulocytes and extravasated erythrocytes.



C.

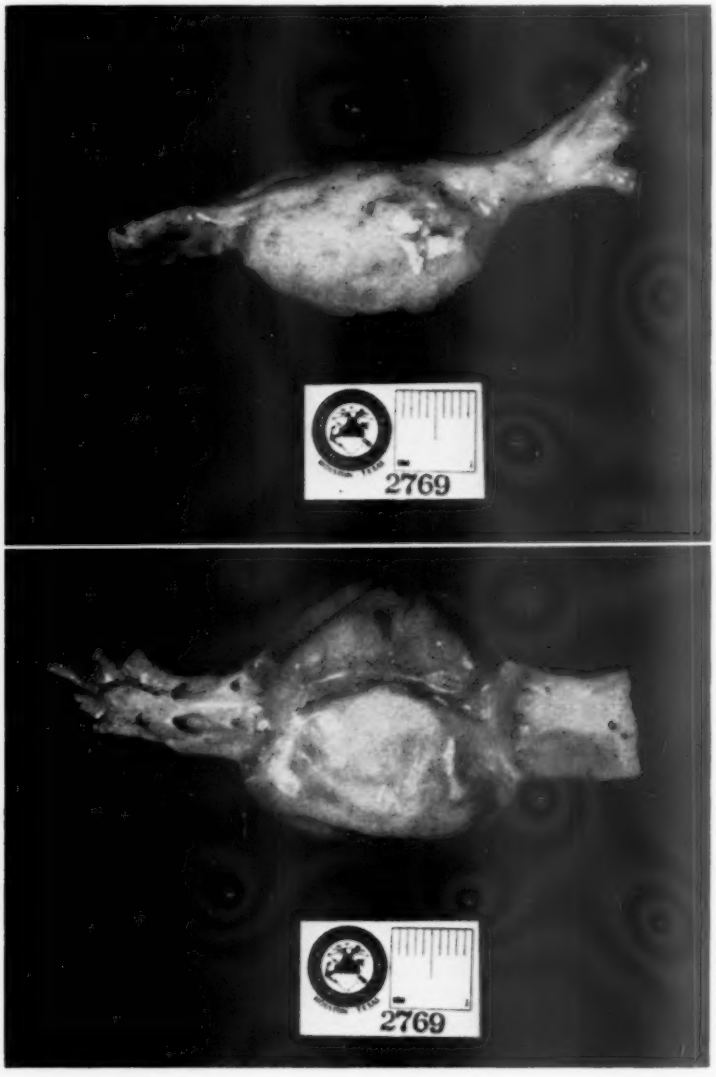
Fig. 2.—*C*, Calcification in the wall of the graft (Weigert's elastic tissue stain). Photomicrograph ×10; reduced ⅙.

One patent thoracic aortic graft examined at seven months was unchanged in diameter. A sheath of fibrous tissue encased the graft and was adherent along the lines of anastomosis. The intimal surface was smooth. The sutures were visible through a transparent layer that covered the anastomoses. Microscopically, the intima was cellular and broadened. The anastomoses were healed by scar tissue. The media appeared compressed and slightly wider than the new intima and was composed of a homogeneous, acellular substance and clearly discernible elastic fibers. The adventitia was thickened by newly formed connective tissue. There was revascularization of the adventitia and of the outer portion of the media.

Four patent, nondilated grafts were examined twenty-four, twenty-five, twenty-six, and twenty-eight months, respectively, following transplantation. They were covered with a dense connective-tissue sheath. The walls were stiff, and 1 graft was rigid. One graft contained a mural thrombus that extended into the host vessel at both ends. The remaining 3 transplants had smooth intimal surfaces (Fig. 2, *A* and *B*). Microscopic examination of these grafts dis-

closed an intimal zone of varying width comprising one-fourth to one-half of the wall (Fig. 2, *C*). In this zone there was an inner band of closely packed wavy fibrils with elongated cell nuclei and an outer band of coarse collagenous bundles in an interlacing pattern with occasional nuclei. Within this zone there were accumulations of blue granules, apparently calcium, and a pink ground substance resembling osteoid. The media was composed of wavy elastic fibers

A.



B.

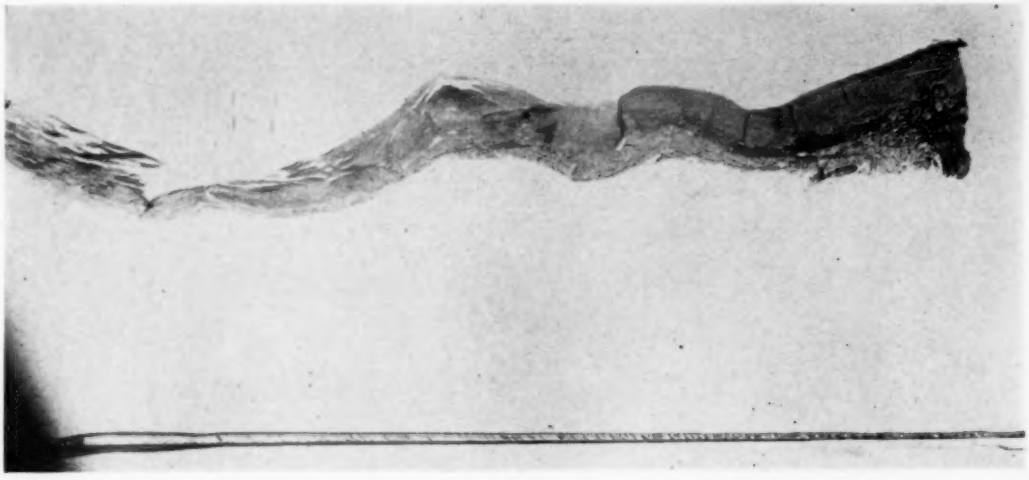
Fig. 3.—*A*, Formalin-fixed graft with sacciform aneurysm twenty-three months after transplantation.

B, Dilatation of the graft begins several millimeters from the lines of anastomoses.

and was thinned or partly interrupted by calcific deposits extending from the intima. The adventitia was made up of loose connective tissue containing thin-walled blood vessels and nerve fibers. At the anastomoses there was a sudden decrease in width of the wall of the grafts compared with that of the host aorta

at either end. The suture lines were surrounded by cellular reaction composed of lymphocytes, plasma cells, large mononuclear cells, and giant cells of the foreign-body type.

The 4 dilated grafts were examined twenty-three, twenty-three, twenty-four, and twenty-six months, respectively, following transplantation. The dilatation was fusiform in 2 and sacciform in 2 (Fig. 3, *A*). The reaction about these grafts appeared to be less pronounced than that surrounding the nondilated grafts. Dilatation was observed to begin 0.3 to 0.5 cm. from the lines of anastomosis (Fig. 3, *B*). The walls of the aneurysms were thin and in one instance almost transparent. Red-orange plaques were noted on the otherwise smooth intimal surface of 1 graft. Microscopic examination of these grafts at their center disclosed focal thinning of the wall (Fig. 3, *C*). Beginning at the anastomoses and proceeding for less than 1 cm. there was a hyaline-like fibrillar intimal zone. Beyond that the intima and media blended into an acellular amorphous fibrillar substance of varying width. In the media there was extensive



C.

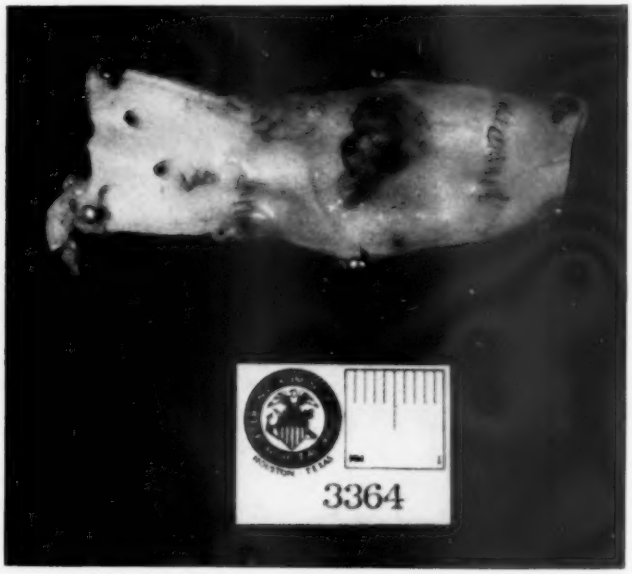
Fig. 3.—*C*, Microscopically, disappearance of the elastic fibers is noted at the site of aneurysmal dilatation (Weigert's elastic tissue stain). Photomicrograph ×10; reduced ⅔.

hyaline change. No nuclear staining was discernible, and the elastic fibers were inconspicuous. In the inner portion of the media, there were many slitlike spaces between elastic fibers. The media contained numerous calcific deposits. The adventitia was composed of connective and adipose tissues. At the anastomoses, double refractile bodies represented the suture material. There was interruption of elastic fibers and change of their course on the host side. The healing of the anastomoses was by hyalinized connective tissue. A fluid coagulum was observed separating the elastic fibers in the media. The adventitia was broadened and composed of loose connective tissue comprising one-fourth of the width of the vessel wall. It contained lymphocytes, plasma cells, and large mononuclear cells. New blood vessels were noted in the adventitia.

Two patent freeze-dried grafts (Group II) of normal diameter were studied eighteen and twenty months, respectively, after transplantation. Grossly, they were encased in dense fibrous tissue derived from adjacent host tissues. The walls were stiff. Except for a 0.5 cm. erosion in one graft (Fig. 4, *A*), the intimal surfaces were smooth and the lines of anastomoses well covered. Microscopic examination disclosed changes similar to those observed in formalin-preserved heterografts. At the erosion site, the intima and about two-thirds of

the media were destroyed (Fig. 4, *B*). Sheets of extravasated erythrocytes were seen between the new adventitia and media, splitting the latter in places. A cellular reaction surrounded the collections of erythrocytes.

Examination of 2 dilated freeze-dried grafts eighteen and nineteen months, respectively, after transplantation disclosed fusiform dilatation in both grafts



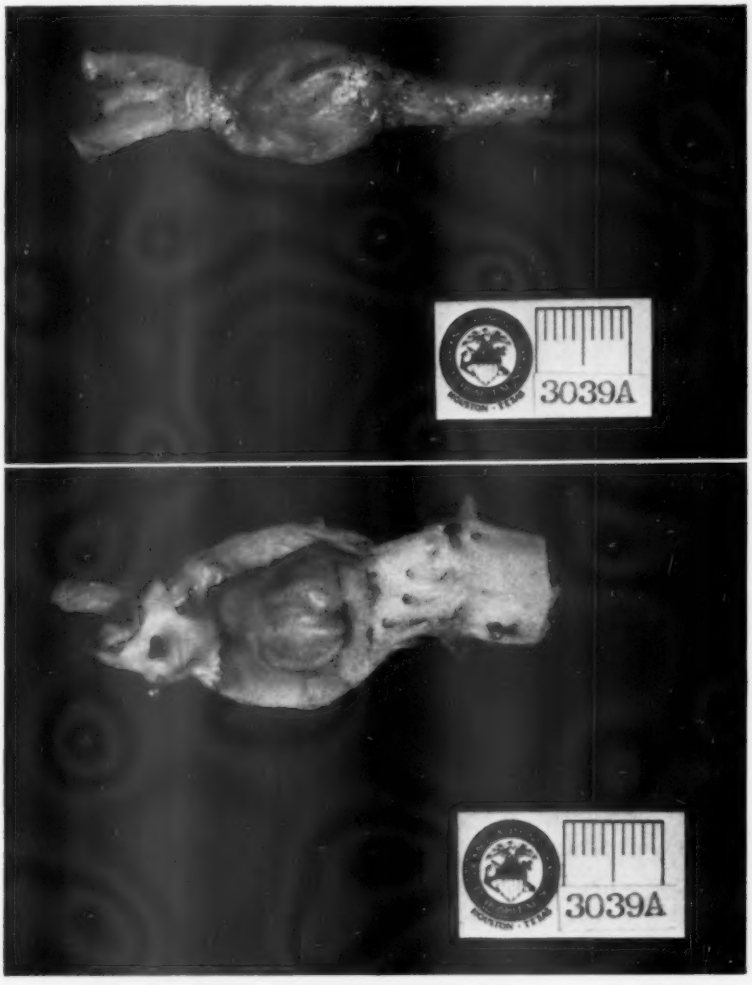
A.

B.

Fig. 4.—*A*, Freeze-dried graft twenty months after transplantation with erosion in the center.

B, Microscopic appearance of the site of erosion. Only a few elastic fibers remaining are in the media. (Weigert's elastic tissue stain). Photomicrograph ×10; reduced ⅙.

A.



B.

C.

Fig. 5.—*A*, Freeze-dried graft eighteen months after transplantation with fusiform dilatation.

B, Dilatation of the graft begins several millimeters from the lines of anastomoses.

C, Microscopically, there is absence of elastic fibers in the dilated portion of the graft. Photomicrograph ×10; reduced ⅙.

that began 0.3 to 0.5 cm. from the anastomoses (Fig. 5, *A* and *B*). In the area of dilatation the walls were thin. On microscopic examination the changes were similar to those observed in the dilated formalin-fixed grafts (Fig. 5, *C*). A hyaline-like fibrillar intima and amorphous media with inconspicuous elastic fibers blended to make up the central dilated portion of the graft. Elsewhere the wall was thicker, and the elastic fibers were better preserved.

The 15 constricted grafts in Group I and 1 thrombosed graft in Group II were examined at necropsy. The reaction about these grafts was more pronounced than that observed about the patent grafts. This was particularly true of the carotid transplants, which were encased in dense scar tissue. In 3 instances the grafts could not be definitely identified, and appeared to have been destroyed by the host.

COMMENT

The results of our studies confirm those of earlier investigations[1-3, 7, 8, 16-18] and serve to re-emphasize the different fates of homografts and heterografts. Replacement of the homograft by host tissues begins at once and is completed in about five months after transplantation. A new intima is formed on the inner surface of the graft by cellular growth from the ends of the host vessel. Although nuclear staining disappears from the media, the elastic fibers remain intact. The adventitia is re-formed from near-by connective tissue. About one year after transplantation the homograft appears grossly and microscopically as a new vessel formed about an elastic tissue framework with a thickened intima, a compressed media, and a broad adventitia. No retrogressive changes were noted in a human homograft one year after transplantation,[4] although calcium deposits have been observed in the media of experimental homografts one to two years old.

The fate of heterografts is that of gradual deterioration rather than replacement and restoration. The early changes are similar to those observed in homografts with the exception that the inflammatory reaction in the adventitia is more pronounced. By the seventh month the elements of the media have begun to deteriorate with extensive areas of hyaline change and calcium deposits.

One-half of the 16 heterografts were dilated when eighteen months or older, a complication rarely encountered in homografts. The gradual diminution and final disappearance of elastic fibers, the principal supportive element of the wall of the vessel, result in dilatation. This occurs in the center of the graft, while near the proximal and distal ends the diameter of the graft remains unaltered. Microscopic studies revealed that here the elastic fibers remained unchanged, providing sufficient strength to prevent dilatation.

In the media of the nondilated grafts, there appeared extensive retrogressive changes, such as calcific deposits and osteoid formation. In the grafts of normal diameter, elastic fibers remained.

The cause of thrombosis in all the carotid heterografts is not apparent. Technical difficulties in working with a vessel of such caliber may have been a contributing factor. The intense host reaction to all these grafts, in some instances amounting to destruction of the graft, suggests that after early occlusion the transplants are rejected by the host.

Implantation of heterologous arteries in human subjects was reported by Oudot[13] in 1949 and more recently by Hufnagel and associates.[10] The late results of these are as yet unknown. We have used clinically a freeze-dried hog's artery to bridge a defect created by resection of an external iliac artery invaded by carcinoma from adjacent lymph nodes. Arteriography five months later disclosed dilatation of the graft to twice its original diameter (Fig. 6). At necropsy, seven months after operation, the graft was dilated and occluded by a recent thrombus.

Fig. 6.—Aortogram five months after transplantation of hog freeze-dried graft to human left external iliac artery. Graft is dilated to twice its original diameter.

The changes observed in both groups of animals, those with formalin-fixed and those with freeze-dried grafts, were alike; therefore, the method of preservation would not seem to be a significant factor in producing the changes. The observations of Pierce and associates[14] on animals followed up to nine months after transplantation of formalin-fixed homografts to the abdominal aorta of dogs support this view. Calcification was noted in most of the grafts, but in no instance was there any aneurysm formation or large surface erosion. We observed no dilatation of freeze-dried homografts implanted in animals for long periods. It seems, therefore, that the most important factor in the deteriorative

changes in arterial heterografts is the host reaction. Homografts appear to produce a mild host response, permitting connective-tissue replacement and revascularization to proceed simultaneously with disappearance of the cellular elements of the media and of the fibrous tissue elements of the adventitia. During this reparative process, the integrity of the graft is maintained by the elastic fibers. On the other hand, the heterograft deteriorates rapidly with loss of elastic elements before connective-tissue replacement and revascularization take place.

SUMMARY

The feasibility of using arterial heterografts as vascular transplants was investigated. Arteries of hogs were preserved by formalin fixation or by freeze-drying. Of the formalin-preserved grafts, 14 were implanted into the common carotid artery, 8 into the thoracic, and 22 into the abdominal portions of the aorta of dogs. Of the freeze-dried grafts, 12 were implanted into the abdominal aorta of dogs.

Arteriographic and subsequent gross and microscopic studies were made in 26 dogs with formalin-fixed grafts and 8 with freeze-dried grafts, five to twenty-nine months after implantation. Arteriographic studies were made on 3 additional dogs still alive.

All of 13 transplants to the common carotid artery and 3 to the abdominal aorta became occluded. Of 18 patent aortic grafts, 9 were dilated. Gross and microscopic studies of the patent grafts revealed marked retrogressive changes in the media consisting of fragmentation and loss of elastic fibers, hyaline change and deposition of calcium, and marked thickening of the adventitia.

Dilatation of a heterologous artery (hog aorta) transplanted into the external iliac artery of a man was demonstrated by arteriography five months after implantation and confirmed at necropsy two months later.

It is concluded that arterial heterografts preserved by the methods used in these experiments eventually weaken and dilate and are therefore unsatisfactory as vascular transplants.

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DISCUSSION

DR. GEORGE J. D'ANGELO (Durham, N. C.).—Dr. Creech's interesting paper with regard to trial of heterologous grafts emphasizes the need for a graft or bridging material which could be used when homologous grafts are not available. Dr. Grimson and I thought that you would be interested in our studies using a plastic, Vinyon-N cloth. The original work with this material was done by Dr. Blakemore and his group. A tube is made from the cloth by a longitudinal suture line and then placed in a defect created in the abdominal aorta. This has been done in fifteen dogs. Six have now been sacrificed for study. During thirty-eight days the plastic cloth is covered with fibrin, which becomes organized so that the lumen has a glistening appearance. At eighty-six days the microscopic sections of this specimen demonstrate an endothelium lining the lumen of the graft. An aortogram taken at 171 days and others at earlier intervals show no dilatation of the graft. It is our impression that a strut or tube of this plastic cloth may prove feasible for clinical use.

DR. HARRIS B. SHUMACKER, JR. (Indianapolis, Ind.).—I think that Dr. Creech's paper is very important, particularly in view of the fact that we were given a different and much more optimistic view concerning the fate of freeze-dried heterologous grafts by Dr. Hufnagel at the meeting of the American College of Surgeons in Chicago last October.

My associates and I have been interested in the use of inert pliable plastic materials for replacement of arterial segments. We have used thin, finely woven nylon. In order to render it impervious we have utilized two methods. One is to fuse it by heat to a sheet of nonreactive polythene, and the other is to coat it with Lucite. Both have worked well. These thin pliable grafts can be sutured in place in the same way vascular transplants are interpolated.

Up to the present time we have sutured in place fairly long grafts, usually 5 cm. or more in length, in approximately sixty animals. In general they have been quite successful. The incidence of thrombosis has not been great, and such difficulties have been very infrequent except in the case of grafts of small size. Thrombosis has occurred less frequently when everting mattress sutures were employed than when simple over-and-over sutures were used. Up to the present, no dilatation or contracture of grafts has been observed. The arteriograms look good. Histologically a new fibrous aorta is seen to develop about the plastic material.

We have felt sufficiently encouraged by the experimental observations to employ such grafts in several patients. In each, the aortic pathway has remained open.

DR. EUGENE M. BRICKER (St. Louis, Mo.).—I would like to remind the Society of a brief presentation made by Dr. Carl Lischer last year at the meeting in St. Louis. At this time he recounted our experience in the use of autologous grafts of the superficial femoral artery. The presentation of Dr. Creech serves to remind us again of the great advantage that could result from the use of autologous arterial grafts if they were available. In our patients we have used the superficial femoral artery to bridge long gaps in the iliac arterial system on the same side. There have been three such patients. Of course, the use of an autologous graft in this manner requires that the remaining arterial tree be relatively normal

and free from arteriosclerosis. The blood supply to the extremity, of course, is maintained through the profunda femoris. I doubt that such an arterial trade could be carried out safely in individuals with much arteriosclerosis. In these young individuals, however, we have bridged gaps in the common and external iliac arteries of up to seven and eight inches. The superficial femoral artery of the same side was either rotated to fill the gap, or was moved in as a free graft. The blood supply of the extremity in each case remained adequate. The use of the superficial femoral artery in this manner suggests the possibility of its use as an autologous graft in other situtations.

One of our patients had severe postoperative complications including generalized peritonitis and a huge pelvic abscess. Although the arterial graft bridged what was in effect an abscess cavity, the graft survived and functioned normally. This patient has subsequently expired, and microscopic and gross examination of the grafted arterial segment reveals no deviation from normal.

DR. ROBERT E. GROSS (Boston, Mass.).—As Dr. Shumaker has indicated, there has been a little wave of enthusiasm regarding the use of heterologous arterial grafts for human beings. I think it is very important that Dr. Creech and Dr. DeBakey's study has shown just how dangerous such grafts can be. While some heterografts, preserved by various techniques, can give excellent results, in any long series of cases (judging from animal work) there will be all too many failures to make the method very safe for use in man.

It might be of interest to go back for a few moments and review some of the statistics on homologous grafts that we have used in aortic replacements. In a series of over 300 patients operated upon for coarctation of the aorta, we have used aortic homografts in forty-two. There were three deaths in the hospital, unrelated to the grafting. Following discharge from the hospital there was death in one patient six months later, from infection. Whether the patient became infected at the time of operation, we do not know, but from the fact that the patient seemed to be clinically well for some months after leaving the hospital, we are inclined to think that infection arose at a later date.

Of the thirty-eight patients who are alive today, grafts have been in place for periods varying from two months on up to almost six years. Ten of them have been in place for more than four years.

The over-all picture as we see these patients in follow-up visits has been very good. From the hemodynamic point of view, three have had only fair relief of their hypertension, while in thirty-five the pressures are entirely normal in the upper part of the body.

In three cases there have been mild depositions of calcium which can be seen on x-ray films. By frequent x-ray studies, we have seen no dilatation of a graft, or aneurysm thereof, in any patient to date.

As one looks back at this series, there can be no doubt that many of the grafts would show profound histologic changes if they could be examined. Yet, the fact remains that pathways have been established which seem to stand up fairly well for considerable periods of time (as long as six years), and we feel very optimistic about the technique of aortic homografting at the moment.

DR. CREECH (Closing).—We have employed approximately sixty-five aortic homografts clinically and have had an opportunity to study one of them histologically one year after transplantation. In this graft the elastic fibers were well preserved with no evidence of fragmentation, and a new intima and adventitia had been formed from connective-tissue elements. No degenerative changes were noted. Whatever the ultimate histologic fate, Dr. Gross's experience indicates that homografts remain functionally satisfactory for relatively long periods.

I wish to thank the discussors for their contribution to this presentation.

ADDITIONAL OBSERVATIONS CONCERNING THE PHYSIOLOGY OF THE HYPERTENSION ASSOCIATED WITH EXPERIMENTAL COARCTATION OF THE AORTA

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(From the Departments of Surgery and Biochemistry, Vanderbilt University School of Medicine)

IN A previous study,[28] evidence was presented which suggested a renal factor in the hypertension of experimental aortic coarctation. Coarctation of the aorta was produced experimentally by anastomosis of the end of the left subclavian artery to the side of the descending aorta and division of the aorta immediately proximal to the anastomosis as originally suggested by Blalock.[3] The gradually progressive development of hypertension in dogs after this procedure suggested that interference with renal hemodynamics was partially responsible for the occurrence of the hypertension. This concept was strengthened by the fact that reversion of the blood pressure to normal levels in these animals was accomplished by transplantation of one kidney to a site above the level of coarctation and contralateral nephrectomy.

Further studies have been performed to extend the investigation of the physiology of hypertension in experimental coarctation and to add control data in the following ways: (1) by observing the effects of transplantation of one kidney to a site below the level of coarctation and contralateral nephrectomy; (2) by assessing the effects of transplantation of one kidney to a site above the level of coarctation while the other kidney remains in situ below the coarctation; (3) by observing the effects on blood pressure in chronic experiments of 60 to 80 per cent constriction of the aorta at a level just above the renal arteries and, as a control, of complete occlusion of the aorta just below the renal arteries; (4) by investigating in survival experiments the relation between the immediate elevation in carotid pressure associated with severe constriction of the aortic isthmus as observed by Gupta and Wiggers[18] in acute experiments and the gradual development of hypertension in experimental coarctation; and (5) by demonstrating by bio-assay the presence or absence of a pressor substance in the renal vein blood of animals with the hypertension of experimental coarctation of the aorta.

METHODS

In these experiments healthy adult mongrel dogs were used. Food consisted of Purina Dog Chow with daily supplements of milk and horse meat. Free access to water was permitted.

At least one week before experimental coarctation was produced in each animal, one of the carotid arteries was transplanted subcutaneously to facilitate subsequent needle puncture. Blood pressure was determined in the unanesthetized animal by direct puncture of the

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femoral and carotid arteries by a No. 20 gauge needle attached to a mercury manometer. Blood pressures in the femoral and carotid arteries were determined frequently during a seven- to thirty-day period prior to production of aortic constriction. Any dog with a mean blood pressure consistently over 150 mm. Hg was excluded from further study. Pressures in the femoral and carotid arteries were measured frequently for the first three to four weeks following creation of coaretation and thereafter at weekly intervals for periods ranging up to twelve months.

For operative procedures intravenous pentobarbital sodium (30 mg. per kilogram of body weight) was used. Pulmonary ventilation was maintained by means of a mechanical respirator which delivered air through an endotracheal tube. Aseptic surgical technique was used in all operations. Penicillin and streptomycin were occasionally administered postoperatively.

RESULTS

In general, most of the animals which survived the operative procedure and the initial postoperative period remained in good condition. A total of ninety-seven animals were used in these experiments, of which forty-two survived for one month or longer.

Preoperative control measurements of mean pressures in the femoral and carotid arteries fell into a range between 110 and 140 mm. Hg. The carotid pressure was occasionally 5 to 10 mm. Hg higher than the femoral. Following the creation of an aortic constriction, there was a fairly marked disparity in the two pressures in all animals. The femoral pressure usually ranged from 60 to 90 mm. in the first seventy-two hours. During this time the carotid pressure showed little or only a slight rise.

There was a gradually progressive rise in the mean carotid pressure following production of aortic constriction, which reached a plateau in five to seven weeks. It appeared that the hypertensive trend began soon after operation although at least two weeks usually elapsed before the blood pressure was elevated over 150 mm. Hg.

Similarly the mean femoral arterial pressure rose progressively after its initial depression. After about six weeks nearly all animals had femoral pressures at least equal to and occasionally considerably higher than the preoperative control values. The disparity between carotid and femoral pressures in these animals with aortic constriction persisted throughout their course although it decreased in quantity.

Animals With One Kidney Transplanted to a Site Below the Level of Coarctation and Contralateral Nephrectomy.—The purpose of this experiment was to establish a rigid control for the previously reported observation that in animals with the hypertension of experimental coaretation, transplantation of all functioning renal tissue to a site above the coaretation resulted in reversion of blood pressure to normal levels. In this group, five successful preparations were obtained. One of these animals, which was included in a previous report,[28] remained alive and healthy for a period well over two years. Following the establishment of normal control pressures in these animals, the right kidney was transplanted to the groin by a modification of the method of Glenn, Child, and Heuer.[13] The renal vessels were divided close to the aorta and vena cava. The ureter was mobilized sufficiently to permit the kidney to be placed in the groin. End-to-end suture anastomoses of the renal and femoral vessels were performed. The kidney was placed under the skin in the groin. Peritoneum and abdominal musculature were closed loosely about the renal pedicle. For the first few days postoperatively, penicillin and streptomycin were administered. Three to ten days following the transplantation, contralateral nephrectomy was performed.

Usually within seven to ten days following contralateral nephrectomy, coarctation of the aorta was produced by the method of subclavian aortic anastomosis.

These animals are not absolutely comparable to those in which a kidney was transplanted to the neck after the hypertension associated with experimental coarctation had manifested itself. However, previous experiments with attempts to transplant a kidney to the groin following production of coarctation were with one exception uniformly unsuccessful.

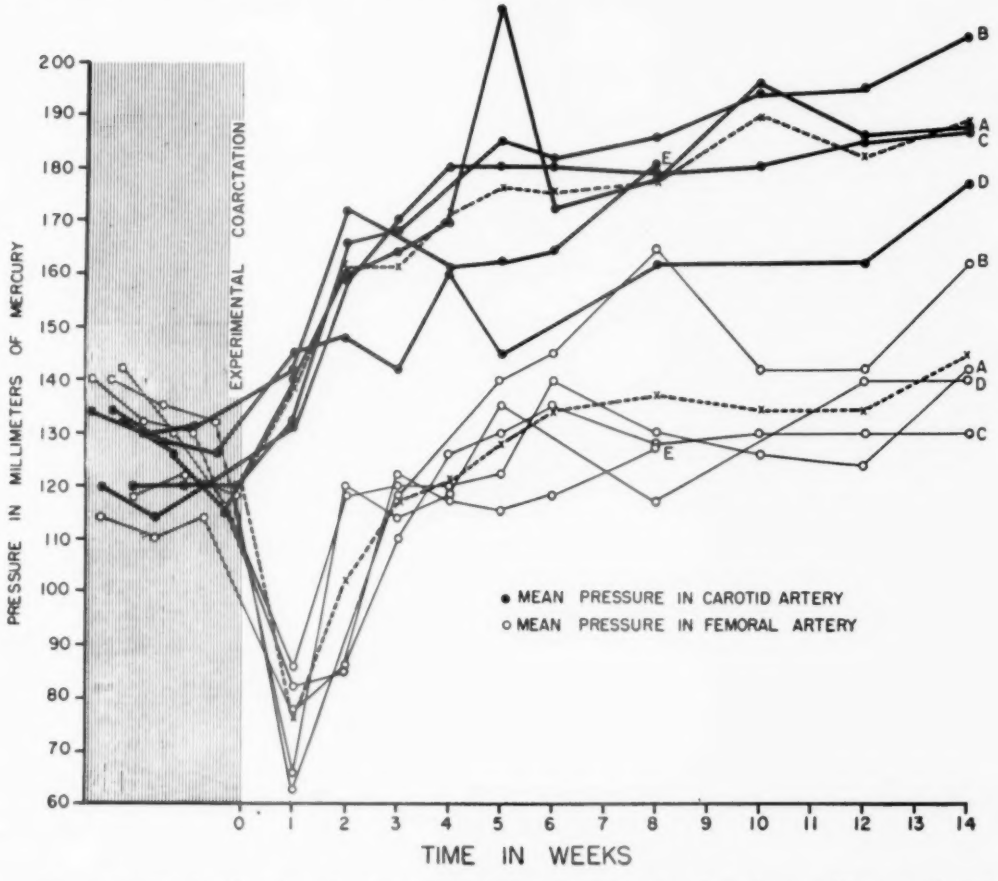

Fig. 1.—Graph showing development of hypertension in five dogs with experimental coarctation of the aorta following transplantation of one kidney to the groin and contralateral nephrectomy. Interrupted lines are calculated mean curves of carotid and femoral pressures.

It was found that in all five animals transplantation of one kidney to the groin combined with contralateral nephrectomy exerted no demonstrable effect upon the development of hypertension in the usual fashion following creation of coarctation. Fig. 1 is a composite graph demonstrating the blood pressure changes in all five dogs before and after production of the aortic constriction. It may be seen that the carotid mean arterial pressure demonstrates a gradual progressive ascent for five to seven weeks, following which it is maintained at a fairly stable hypertensive level. The femoral pressure, after an initial depression, also rises and stabilizes within five to seven weeks.

In one of these animals, with hypertension well established after creation of coarctation, the kidney was removed from the groin and transplanted to the neck. Following this procedure there was a return of the blood pressure to preoperative levels (Fig. 2).

Animals With One Kidney Transplanted to a Site Above the Level of Coarctation and the Other Kidney in Situ.—The purpose of this experiment was to answer the following questions: (1) Is the disappearance of hypertension following transplantation of all functioning renal tissue to a site above the level of coarctation due to the function of the transplanted kidney as an arteriovenous fistula? (2) Will the hypertension of experimental coarctation disappear if one kidney is transplanted to a level above the coarctation while the other kidney remains in situ below the coarctation?

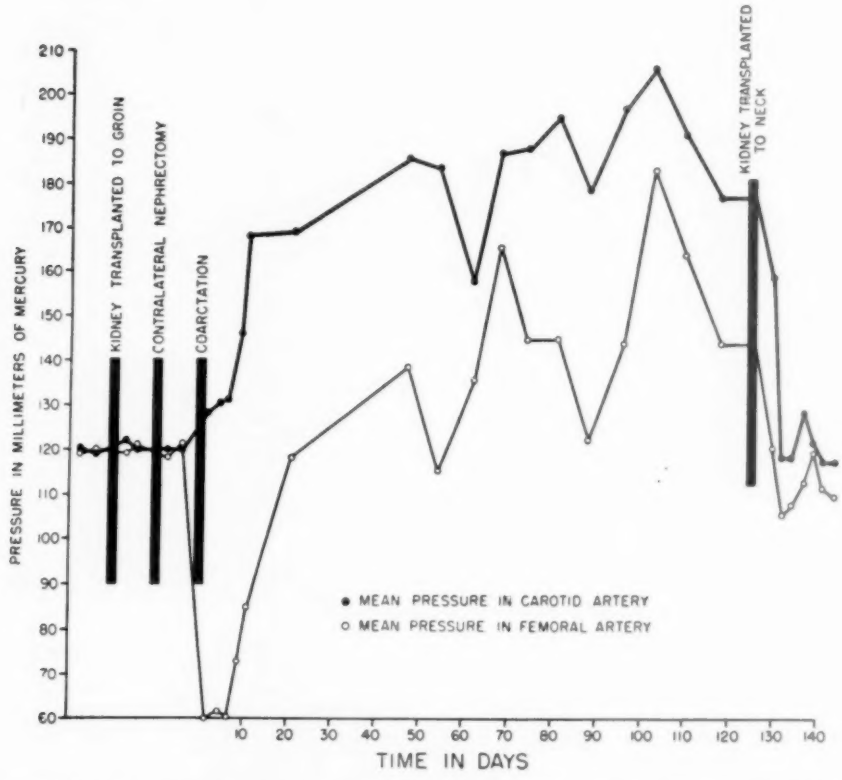

Fig. 2.—Graph showing development of hypertension in a dog with experimental coarctation of the aorta following transplantation of one kidney to the groin and contralateral nephrectomy. The mean carotid pressure is returned to a normotensive range by transplantation of the single kidney from a level below to a level above the coarctation.

In this group of animals, aortic constriction was produced after a sufficient number of control blood pressures had been obtained. When a sustained hypertensive "plateau" had become established after production of coarctation, one of the kidneys was transplanted to the neck by the method of Carrel,[6] as in the previous study. This consisted of mobilization of the external jugular vein and carotid artery through a vertical incision in the neck. The kidney was approached through a flank incision. As much length as possible of the renal vessels was obtained, and they were divided as was the ureter. An end-to-end suture anastomosis was made between the ends of the carotid and renal arteries and of the external jugular and renal veins. The cervical skin was undermined, and the kidney was buried subcutaneously. The end of the ureter was exteriorized through a stab wound, and a short length of polyethylene tubing was inserted into the end and tied in place. All dogs were given penicillin and streptomycin for a few days postoperatively.

There were six animals in this group which survived for at least three weeks following transplantation of one kidney to the neck. Three of these six dogs had coarctation produced by the method of subclavian aortic anastomosis. Two of the remaining three had aortic constriction produced by "wedging" the supradiaphragmatic portion of the aorta. The remaining dog had constriction produced by "wedging" in the region of the aortic isthmus. The method of wedging used for production of aortic coarctation will be discussed in detail later.

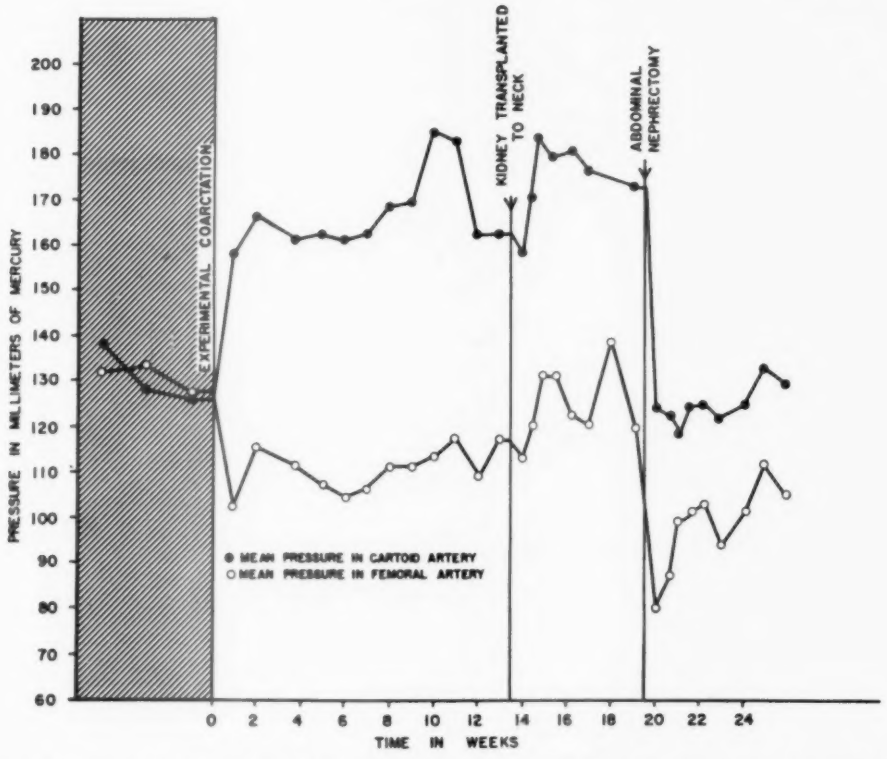

Fig. 3.—Graph showing maintenance of hypertension after cervical renal transplantation and later disappearance of hypertension following contralateral nephrectomy in one dog with experimental coarctation.

All these animals had a moderate to marked hypertension six weeks following production of aortic constriction and prior to cervical transplantation of one kidney. Following the transplantation, frequent blood pressure determinations were made in one dog for eight weeks, one for six weeks, three for four weeks, and one for three weeks. In four animals, cervical transplantation of one kidney had no apparent effect upon the sustained high level of either the carotid or femoral mean arterial pressures. In two animals there was a slight to moderate decrease in both carotid and femoral mean arterial pressures following transplantation of the kidney to the neck. These decreases were maintained for six and eight weeks, respectively, at the end of which time the transplanted kidneys were excised. Following excision of the transplanted kidneys, the blood pressure remained in the same general range in both dogs for two months, after which they were sacrificed. The fact that there was no change in the blood pressure following excision of the transplanted kidneys casts doubt upon the significance of the observed decrease.

After the cervically transplanted kidney had been in place for four weeks in two dogs and three weeks in one dog with no discernible effect upon the level

of the blood pressure, the kidney remaining in the abdomen was excised. Following this, one dog lived for one week, one for two weeks, and the other died at the end of five weeks. Abdominal nephrectomy caused a prompt (within four to seven days) reversion of the blood pressure to normal levels in each animal (Fig. 3). Nonprotein nitrogen of the plasma was persistently elevated in these animals, ranging from about 50 to 80 mg. per cent. The values, however, remained fairly stable until terminal changes occurred.

The remaining dog in this group died four weeks following transplantation of one kidney to the neck and immediately after blood for bio-assay had been withdrawn from the renal vein of the abdominal kidney. Results of the bio-assays in these dogs will be presented later.

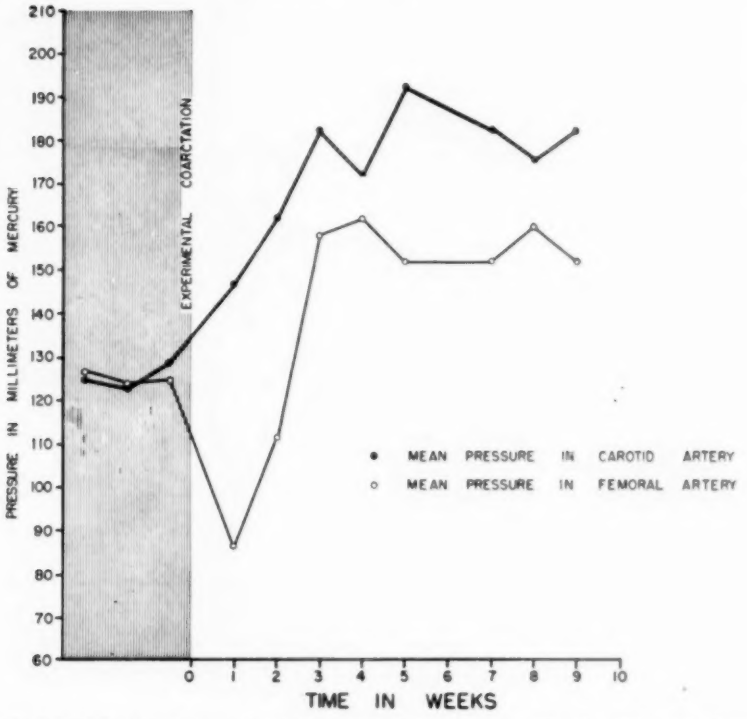

Fig. 4.—Graph showing development of hypertension in one animal with experimental coarctation at a level just superior to the renal arteries.

Animals in Which Aortic Constriction Was Performed at a Level Just Above the Renal Arteries by the Method of "Wedging."—The purpose of this study was to determine in chronic experiments the effect that the level of aortic constriction in relation to the origin of the renal arteries exerts on blood pressure. In this group of animals, constriction of the aorta was performed by a modification of Clatworthy's method.[7] Clatworthy originally used young dogs and excised a wedge of the aorta in the region of the isthmus. He sutured the aortic edges together and wrapped the wedged segment with a strip of polyethylene film. By using young dogs, he took advantage of the differential growth gradient of the aorta. In his hands the method was quite efficacious in producing a condition very similar to clinical coarctation.

We have used the method in adult dogs in which we have excised a wedge of aorta comprising 60 to 80 per cent of the aortic diameter, just superior to the diaphragm. Initially we injected a solution of dicetyl phosphate into the adventitia of the wedged segment. We later abandoned this practice since it

was felt that increasing blood pressures might possibly be due to increasing fibrous reaction about the wedged segment. Actually, at autopsy it has been difficult to attribute any increased fibrous tissue reaction to the dicetyl phosphate.

The method of wedging has been used successfully for the production of aortic constriction just superior to the diaphragm in nine dogs. Performance of aortic constriction by this method resulted in moderate to marked sustained carotid and occasionally femoral hypertension in six of the surviving dogs (Fig. 4). We have been impressed by the fact that the carotid hypertension in these animals has tended to manifest itself earlier and to stabilize sooner after production of constriction than in those animals in which the constriction is at a higher level.

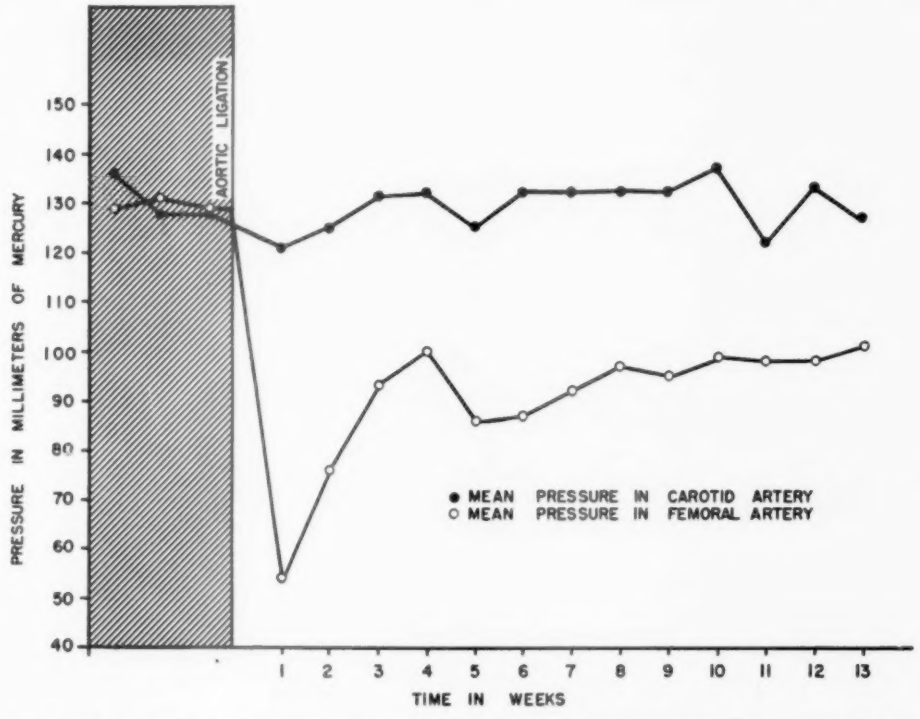

Fig. 5.—Graph showing calculated mean curves of carotid and femoral pressures in five dogs with aortic ligation inferior to the renal arteries.

Three of the surviving dogs manifested a transient mild brachiocephalic hypertension. This was usually apparent within two to three weeks after production of the aortic constriction and had disappeared within six weeks. It was demonstrated that in all of these animals, less than 50 per cent occlusion of the aorta had been obtained.*

Animals With Division of Aorta Inferior to Origin of the Renal Arteries.—The aorta was completely divided just inferior to the origin of the renal arteries in six dogs to serve as a control for the experiments in which constriction of the aorta had been produced just superior to the origin of the renal arteries. In this group the aorta was mobilized in the region just inferior to the origin of

*In these dogs a slightly larger wedge of aorta was excised from the region of the previous operation. One of these animals died immediately postoperatively. One of them demonstrated no hypertensive trend at the end of five weeks and was sacrificed. At autopsy it was found that despite two operations, only 40 per cent of the aortic diameter had been occluded. The remaining dog demonstrated a fairly prompt and marked elevation in both carotid and femoral arterial pressures following the second operation but expired at the end of three weeks.

the renal arteries and divided between Potts patent ductus clamps; the aortic ends were sutured by Swan's technique.[33]

One dog did not survive operation. The remaining five dogs all demonstrated a transitory flaccid paralysis of the hind legs for the first two to three days. All recovered promptly except one, which continued to demonstrate slight weakness at the end of three months. Carotid and femoral arterial pressures were determined in these dogs at weekly intervals for three months. The femoral pressure was markedly reduced immediately after operation in each case, and it was frequently difficult to measure for the first two to three weeks. After that time the pressure had usually increased to 70 to 80 mm. Hg and by the end of three months was usually in the range of 90 to 100 mm. Hg. In contrast to this, the carotid mean arterial pressures showed little significant deviation from the preoperative control range (Fig. 5).

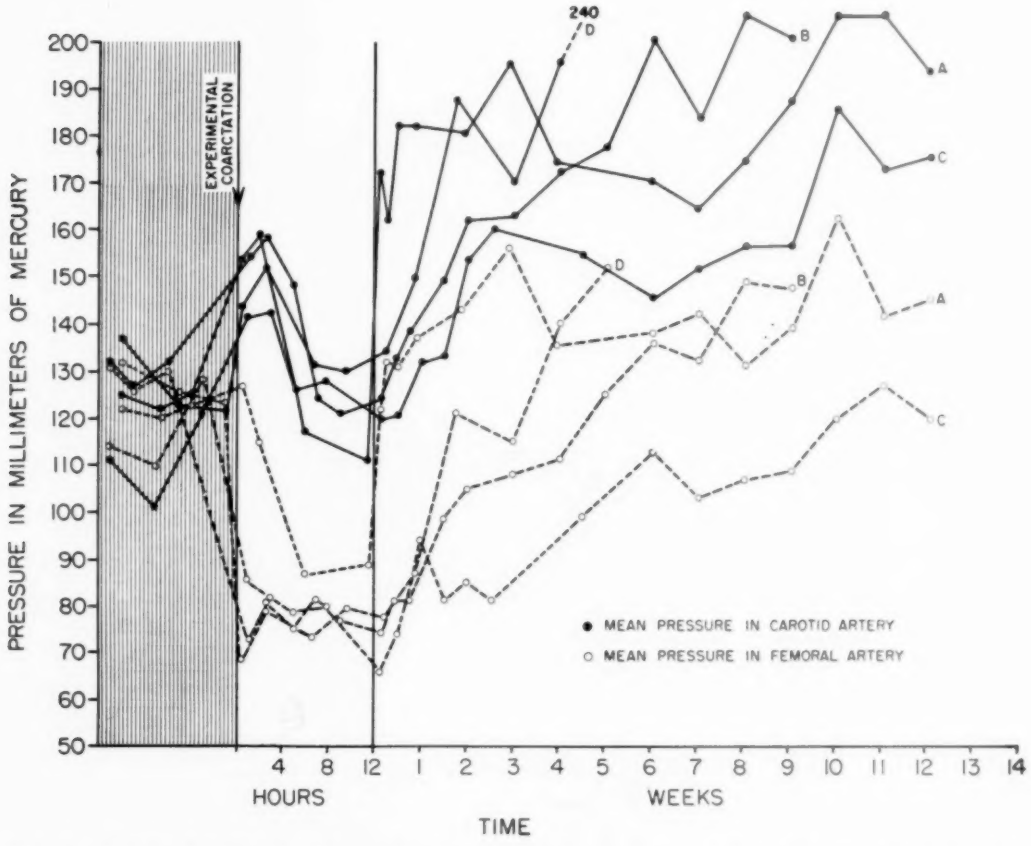

Fig. 6.—Graph showing initial transient hypertensive response followed by gradual development of sustained hypertension in four dogs with experimental coarctation of the aorta.

Animals in Which Multiple or Continuous Arterial Pressure Recordings Were Made in the Immediate Postoperative Period Following Production of Coarctation and Following Complete Occlusion of the Aortic Isthmus.—In order to study the relation between the immediate elevation in carotid pressure associated with severe constriction of the aortic isthmus as observed by Gupta and Wiggers[18] in acute experiments and the gradual development of hypertension in experimental coarctation, two group of animals were used. In one group of six dogs, experimental coarctation was produced by the method of subclavian-aortic

anastomosis, and arterial pressures were recorded at frequent intervals in the first twenty-four hours following operation and thereafter at daily intervals until chronic hypertension was well-established. The changes in carotid and femoral arterial pressures in this group of animals are demonstrated in Fig. 6. Immediately following production of experimental coarctation there was a moderate rise in the level of carotid pressure; however, this elevation was sustained for only a few hours after operation. Preoperative levels of carotid pressure were then observed for several days with a gradual rise to hypertensive levels.

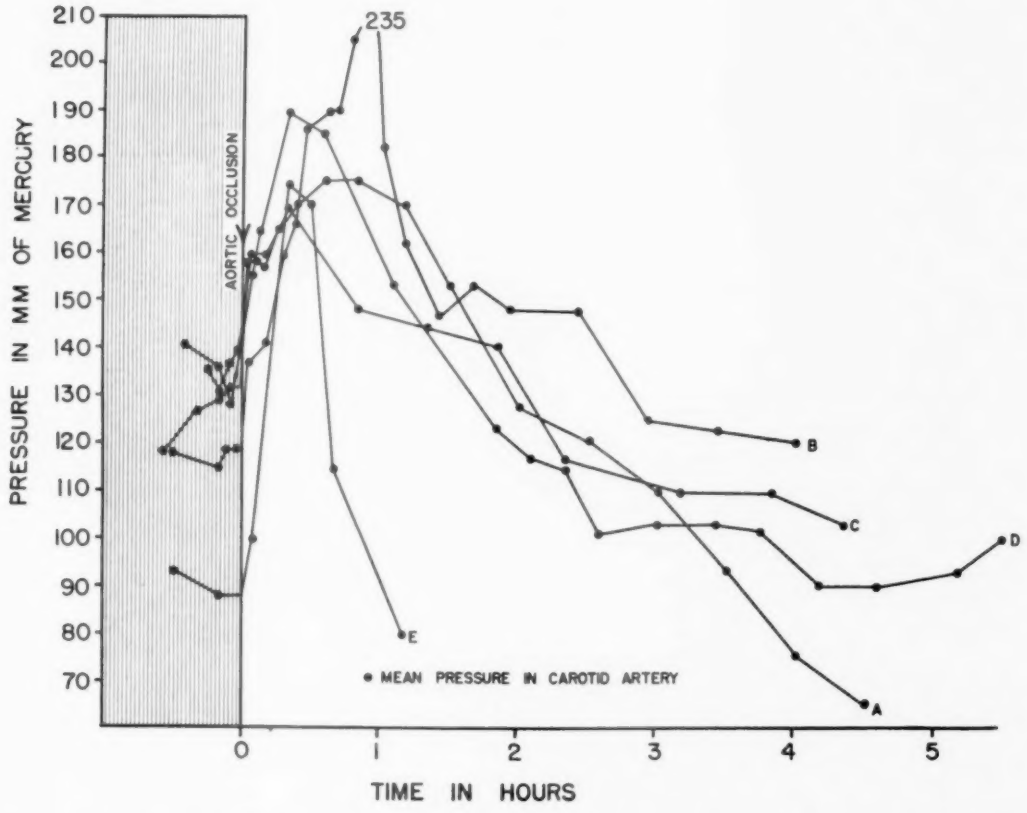

Fig. 7.—Graph showing transient hypertension observed after ligation of aortic isthmus in five dogs.

In a second group of five dogs, continuous recordings of carotid and femoral arterial pressures were made during the total survival period after complete occlusion of the aorta immediately below the origin of the left subclavian artery. In three of these animals the chest was opened, the aorta was occluded by ligation, the lungs were re-expanded, and the chest was closed. In two other animals a Bethune tourniquet was applied to the aortic isthmus, and aortic occlusion was deferred until forty minutes after re-expansion of the lungs and closure of the chest. The changes in carotid and femoral pressures in these animals are illustrated in Fig. 7. The sharp rise in carotid mean pressure which occurred with abrupt, complete aortic occlusion persisted for only thirty minutes to two hours in these animals. Carotid mean pressure then returned gradually to pre-occlusion levels and was quite stable at these levels until the rather sudden death of the animal a few hours later.

Animals in Which Bio-assay for Pressor Substances Was Performed Upon the Renal Vein Blood.—In further elucidation of the role of the kidney in the hypertension associated with experimental coarctation, bio-assay for pressor substances was performed upon the renal vein blood in six animals. Chemical extraction and bio-assay were performed by the method of Schroeder and Olsen.[22, 27] The presence of a pressor substance designated "pherentasin" is demonstrated by this method. Pherentasin has been found chiefly in patients with the "renal" type of hypertension and is ordinarily absent in normal control subjects and in those with hypertension due to other causes. In a previous study (unpublished data) the substance could not be demonstrated in normal dogs.

In one animal with the hypertension of experimental coarctation, bio-assay was performed before and after transplantation of one kidney to the neck and contralateral nephrectomy. The five other animals with aortic constriction in which bio-assay was accomplished included three dogs with a single kidney situated in the groin and two dogs in which abdominal and cervical kidneys coexisted.

Blood for bio-assay was obtained by exposing one of the renal veins. Direct venipuncture was performed using a No. 18 gauge needle attached to a syringe and short piece of polyethylene tubing through a stopcock. Approximately 500 ml. of blood was obtained from the renal vein in this fashion and delivered into a flask of cold alcohol. At the conclusion of the phlebotomy, a suture was usually taken in the vein to prevent further bleeding. Thirty to sixty minutes prior to phlebotomy, a 500 ml. whole blood transfusion was started. The transfusion and phlebotomy were ordinarily completed almost simultaneously.

The results of bio-assay in the six animals studied to date may be seen in Table I. Pherentasin activity was moderate to marked in two of the three animals in which the groin kidney was the only kidney. Bio-assay was performed on one of these dogs (No. 329) during a period when his usually elevated carotid pressure was in the normotensive range coincident with extensive infected lacerations following a dog fight. No detectable pherentasin was present. The cause for this decline in the hypertension associated with altered renal hemodynamics during infections is unknown, but it has been observed by other investigators.

TABLE I. RESULTS OF BIO-ASSAY FOR PRESSOR SUBSTANCE (PHERENTASIN) ON RENAL VEIN BLOOD IN ANIMALS WITH EXPERIMENTAL COARCTATION

DOG NO.	DATE	CAROTID MEAN PRESSURE AT TIME OF BIO-ASSAY	REMARKS	PHERENTASIN
445	Feb. 23	220	One kidney; in groin	++
467	March 17	190	One kidney; in groin	+
329	May 8	125	One kidney; in groin	–
47	June 1	194	Both kidneys in situ	++
	July 13	124	One kidney; in neck	–
24	July 7	170	One kidney in neck, one kidney in situ	–
	July 21	116	One kidney; in neck	–
1044	July 15	192	One kidney in neck, one kidney in situ	+

Bio-assay was performed in two animals in which cervical and abdominal kidneys coexisted. One of these animals (No. 1044) demonstrated a moderate amount of pherentasin activity, while the other (No. 24) demonstrated none. Following abdominal nephrectomy in No. 24 with consequent decrease of the brachiocephalic blood pressure, bio-assay again failed to demonstrate pressor substance.

Marked amounts of pherentasin in the renal vein blood of No. 47 could be demonstrated by bio-assay when both kidneys were situated below the coarctate segment. Transplantation of one kidney to the neck and contralateral nephrectomy in this animal caused a reversion of the blood pressure to a normal level. Bio-assay of blood from the vein of the transplanted kidney during this period demonstrated no pherentasin.

It may be noted that pherentasin could be demonstrated only in those animals in which the carotid mean blood pressure was at a level of 190 to 200 mm. Hg or higher at the time blood was withdrawn for bio-assay.

DISCUSSION

The physiologic mechanisms involved in the hypertension of human coarctation of the aorta have been explored by numerous investigators. Two generally opposing views concerning the cause of the hypertension in coarctation have resulted from their studies. The first, which may be termed the "mechanical hypothesis," was proposed by Blumgart and his associates[4] in 1931 and has more recently been supported by the work of Bing and co-workers[2] and by Gupta and Wiggers.[18] The advocates of the mechanical hypothesis suggest that the hypertension results from the resistance to blood flow presented by the aortic stricture itself and the collateral vessels. The second view, which may be called the "renal hypothesis," is that the aortic stricture produces a disturbance in renal hemodynamics similar to that of the Goldblatt kidney and that hypertension results from a generalized increase in vascular resistance mediated through a renal mechanism. The renal hypothesis has been advocated by Steele,[31] Rytand,[26] Stewart and Bailey,[32] Page,[23] and others.

The experimental production of coarctation offers an unusual opportunity to investigate the physiology of the hypertension in this disorder. While the constriction of the aorta produced experimentally in this study is not the exact anatomic counterpart of human coarctation, the hemodynamic changes produced resemble those seen in human cases. The measurement of arterial pressures following production of experimental coarctation demonstrates a progressive increase in the carotid mean arterial pressure until a hypertensive "plateau" is reached about five to seven weeks following operation. The femoral mean pressure shows an initial immediate decrease which is followed by a gradual increase to normal or supranormal levels. Similar results have been reported by Blalock[3] and Sealy and McSwain.[30]

The fact that the carotid and femoral mean arterial pressures tend to increase progressively following production of coarctation is difficult to reconcile with a purely mechanical hypothesis concerning the origin of the hypertension. This line of reasoning has been lucidly presented by Harris and associates,[20] who pointed out that the carotid pressure should be highest shortly after the creation of the experimental coarctation if the mechanical hypothesis were correct. The pressure should then decrease because of the development of collateral circulation.

As was previously demonstrated,[28] transplantation of all the functioning renal tissue to a level above the site of experimental aortic constriction causes a prompt reversion of the blood pressure to normal levels. In the present study

it has been shown that this reversion in blood pressure cannot be attributed to alterations in function of the denervated autografted kidney per se or to disturbance of adrenal blood supply. In one animal with experimental coarctation and hypertension, transplantation of one kidney to the groin and contralateral nephrectomy had no effect on the hypertension, which was maintained for two years thereafter. In four other animals it was demonstrated that preliminary transplantation of all functioning renal tissue to the groin failed to prevent the development of hypertension in the usual fashion after subsequent production of coarctation. When the solitary groin kidney is then transplanted to a site above the aortic constriction, a prompt normotensive reaction ensues.

It might be suggested that transplantation of a kidney to the neck in animals with coarctation produces a physiologic arteriovenous fistula with consequent lowering of the mean arterial blood pressure. This tends to be refuted by the following evidence: In animals with experimental coarctation in which one kidney is transplanted to the neck and the other remains in situ, there is little demonstrable change in blood pressure. When the cervical kidney is excised after an appropriate period of time, there results little change in blood pressure. When, however, the abdominal kidney is excised leaving the cervical kidney in place, there is a prompt reduction in the blood pressure.

Apparently, when a sufficient amount of aortic constriction is produced at any site superior to the origin of the renal arteries, brachiocephalic hypertension results. This has been demonstrated by Goldblatt[15] and Rytand.[26] Page[23] was unable to detect any hypertensive trend following constriction of the aortic arch, but his longest period of observation was twelve days. It has since become clear that it requires a longer period of time before the hypertension is manifest when the constriction is at this level.

Complete division of the aorta at a level inferior to the origin of the renal arteries has no effect upon the blood pressure above the level of division. Below the level of division, the pressure falls and tends to remain down or, at most, return to preoperative levels. This is in agreement with the work of Goldblatt.[15]

Gupta and Wiggers[18] have carried out acute experiments in which careful recordings of pressures were made with varying degrees of aortic constriction. They demonstrated that the aortic systolic and diastolic pressures proximal to an acute aortic constriction rise progressively with the degree of constriction after the constriction has reached a degree of 45 to 55 per cent of the aortic lumen. On the basis of these studies they concluded that the hypertension of coarctation could be explained fully by mechanical factors.

It is questionable if valid conclusions concerning the chronic hypertension of coarctation of the aorta can be drawn from acute experiments. In the present study it has been observed tht the immediate elevation of carotid pressure produced by a degree of aortic constriction compatible with long survival persists for only a few hours. This transitory hypertension is certainly "mechanical" in origin. It is superseded in survival experiments by a period of normotension, usually lasting several days, with gradual development of hypertension, which

becomes stabilized and sustained five to seven weeks after operation. The immediate rise in carotid pressure which occurs with complete occlusion of the aortic isthmus also proves to be transitory, as shown by Erlanger and Gasser[9] and confirmed in these studies. There is a return to preocclusion levels of carotid pressure within one to two hours followed by a fairly stable period until the rather sudden death of the animal a few hours later. It seems apparent that the transitory hypertension produced by acute aortic constriction is mechanical in nature, as demonstrated by Gupta and Wiggers; however, this differs from the chronic sustained hypertension of experimental coarctation.

The evidence accumulated from this study demonstrates that the kidneys are intimately concerned in the production and maintenance of the hypertension associated with experimental coarctation of the aorta. These experiments indicate that the mechanical effect of the aortic constriction serves as the stimulus to renal hypertension by altering the hemodynamics below the constriction.

The bio-assay studies are obviously too meager to permit any far-reaching conclusions. It would appear, however, that in any animal with a fairly marked brachiocephalic hypertension associated with experimental aortic constriction, a pressor substance may be demonstrated in the renal vein blood. In one experiment this substance disappeared coincident with reversion of arterial pressure to normal levels after renal transplantation.

Evidence for[31, 32] and against[2, 4, 21] a renal factor in the hypertension of human aortic coarctation has been adduced from investigations of peripheral resistance. The difficulties in interpretation of these types of data have been presented by Harris.[20]

The mechanical hypothesis is inadequate to explain the blood pressure changes following the resection of the coarctation and end-to-end anastomosis of the aorta in patients. It is most unusual to find that the blood pressure returns to normal levels abruptly following operation. The more common thing is to find that several weeks is required for the pressure to stabilize at a normotensive level. Hallenbeck[19] found that only 29 per cent of his surgically treated patients had a normal blood pressure, that is, less than 130/90, one month postoperatively, whereas the number later increased to 49 per cent.

That the kidneys play an important role in the hypertension of human aortic coarctation has been previously advocated. Studies of the renal blood flow in patients with coarctation have usually shown the blood flow to be a low normal value. Genest and his associates[11] have found that there is an increase in the renal blood flow following surgical correction of coarctation. Harris and co-workers[20] believed this change to be transient and stated that the renal blood flow reverts to preoperative levels two to three months following operation. Because of the fact that the blood flows are not strikingly abnormal, it has been suggested that a diminished renal pulse pressure may be the important factor in production of the hypertension.[24, 25] Conclusive evidence for this remains to be presented. Regardless of the specific pathogenesis, it does appear from the experimental evidence and ancillary clinical data that the kidneys are implicated substantially in the etiology of the hypertension associated with coarctation of the aorta.

SUMMARY

The evidence accumulated from this study demonstrates that the kidneys are intimately concerned in the production and maintenance of the hypertension associated with experimental coaretation of the aorta. Production of an aortic constriction superior to the kidneys results in a progressive elevation of the carotid mean arterial pressure to a hypertensive level. After an initial depression, the femoral mean arterial pressure also increases. The transplantation of one kidney to a site below the level of aortic constriction and contralateral nephrectomy does not measurably affect the hypertensive trend following production of aortic coaretation. The hypertensive pattern following production of aortic coaretation is not altered by transplantation of one kidney to a site above the level of coaretation as long as the other kidney remains below the aortic constriction. When the kidney remaining below the aortic stricture is excised, however, there is a prompt reversion of the blood pressure to its preoperative control level. Reduction of the aortic diameter by 60 to 80 per cent immediately superior to the origin of the renal arteries results in the development of hypertension. There is no demonstrable change in the level of brachiocephalic blood pressure following complete division of the aorta immediately inferior to the origin of the renal arteries. The immediate elevation of carotid pressure produced by acute aortic constriction persists for only a few hours and is mechanical in origin. This differs from the chronic sustained hypertension of experimental coaretation. The results of bio-assay on renal vein blood in animals with experimental coaretation of the aorta suggest that the associated hypertension is renal in origin.

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DISCUSSION

DR. STANLEY W. WIDGER (Rochester, N. Y.).—I would like to commend Dr. Scott on his clever method in attacking this fascinating problem.

EXTENSION OF IMMEDIATE CHOLANGIOGRAPHY IN COMMON DUCT SURGERY

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THE use of operative cholangiography in surgical investigations of the biliary system is well established.[1-3] It has been because of certain technical difficulties that its usage has not become widespread or completely acceptable. The present study was undertaken in an attempt to assay and correct technical difficulties associated with cholangiography as encountered in the usual hospital practice and to extend the method to encompass those conditions in which it has not been widely utilized.

We have directed our attention toward an investigation of the contrast media, the various biliary calculi and artifacts, and a simplified method of cholangiography. Extensions of our method have been applied to biliary surgery in both the newborn child and the adult.

CONTRAST MEDIA AND CALCULI

By the use of both an artificial biliary system utilizing rubber tubing in the forms of a commonly used intravenous tubing and Penrose tubing, along with autopsy material, the following studies were carried out (Fig. 1).

A comparison of iodized aqueous solutions and iodized oily solutions was made. It was found that the aqueous solution possessed definite advantages over the oily solution largely because of the latter's viscosity. The high viscosity of oily solution made injection more difficult, complete filling of the duct system was less easily accomplished, and air bubbles were frequent.

It thus became apparent that the aqueous solution was more acceptable, and iodopyracet (Diodrast)* was adopted.

A comparison of the preparations of Diodrast was then undertaken. In the higher concentration, 70 per cent, smaller stones tend to be obscured by the density of this medium. The 35 per cent solution of Diodrast was found to be more advantageous, but radiographic visualization of the calculi in the artificial system, particularly of the smaller calculi, was impaired when the tubing was distended. The relative difference in density between the stone and the contrast medium was thus obscured by an increased quantity of the radiopaque solution. This objection was not apparent in the case of large stones. The effect of air bubbles within the artificial system was also considered. Air bubbles produce a space-occupying defect difficult to distinguish from calculi. Were it not for

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*Diodrast, Winthrop-Stearns, Inc.

the uniformly rounded appearance of the bubbles, their tendency to cluster, and the advantage of a two-film technique, calculi and bubbles would be indistinguishable. It is recognized that air bubbles in the medium may constitute a serious source of confusion.

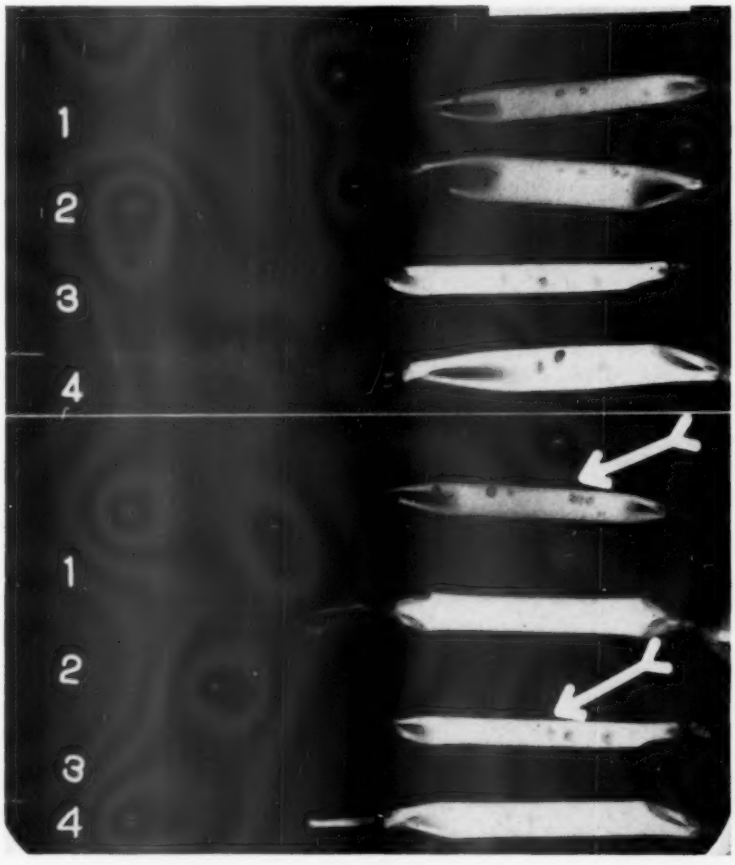

Fig. 1.—Simulated common bile ducts containing gallstones. Four similar stones have been placed on each side of the tied, thin-walled rubber tubing. No media in left segments.

1, Three-eighths inch tubing containing four small stones and Diodrast 35 per cent.

2, One-half inch tubing containing four small stones and Diodrast 35 per cent.

3, Three-eighths inch tubing containing four medium-sized stones and Diodrast 70 per cent.

4, One-half inch tubing containing four medium-sized stones and Diodrast 70 per cent.

Lower exposure represents the same tubes, stones, and media except:

1, Air bubbles have been introduced into the tubing (as indicated by the arrow). The stones and air bubbles are quite similar.

2, The tubing is distended with media (Diodrast 35 per cent). The stones are almost invisible.

3, Air bubbles have been introduced into the media and cannot be differentiated with certainty.

4, The tubing is distended with media (Diodrast 70 per cent). Medium-sized stones are only faintly visible.

Stones of a high calcific content were also investigated in the artificial system. The possibility of a stone having sufficient density to blend with the media and thus become indistinguishable was considered, but such a stone would usually be known clinically from preliminary radiographic studies. In calcific stones there is usually a layer of cholesterol on the periphery which permits detection of its outline in the contrast medium.

TECHNIQUE OF OPERATING ROOM CHOLANGIOGRAPHY

There are several techniques for performing operating room cholangiography. Perhaps the most widely used is that of positioning the patient appropriately upon the operating table with a wooden cassette tunnel beneath the patient's upper abdomen. The bedside radiographic unit is wheeled beside the operating table, the tube placed over the operative field, and the film exposure is made from above. Another technique includes having a Potter-Bucky grid apparatus built into the table with the same manner of exposure. The necessary common factors in all techniques are a nonexplosive anesthetic mixture, a suitable contrast medium, sufficient distance, freedom from radiopaque instruments and equipment in the field at the time of examination, and minimal patient motion.

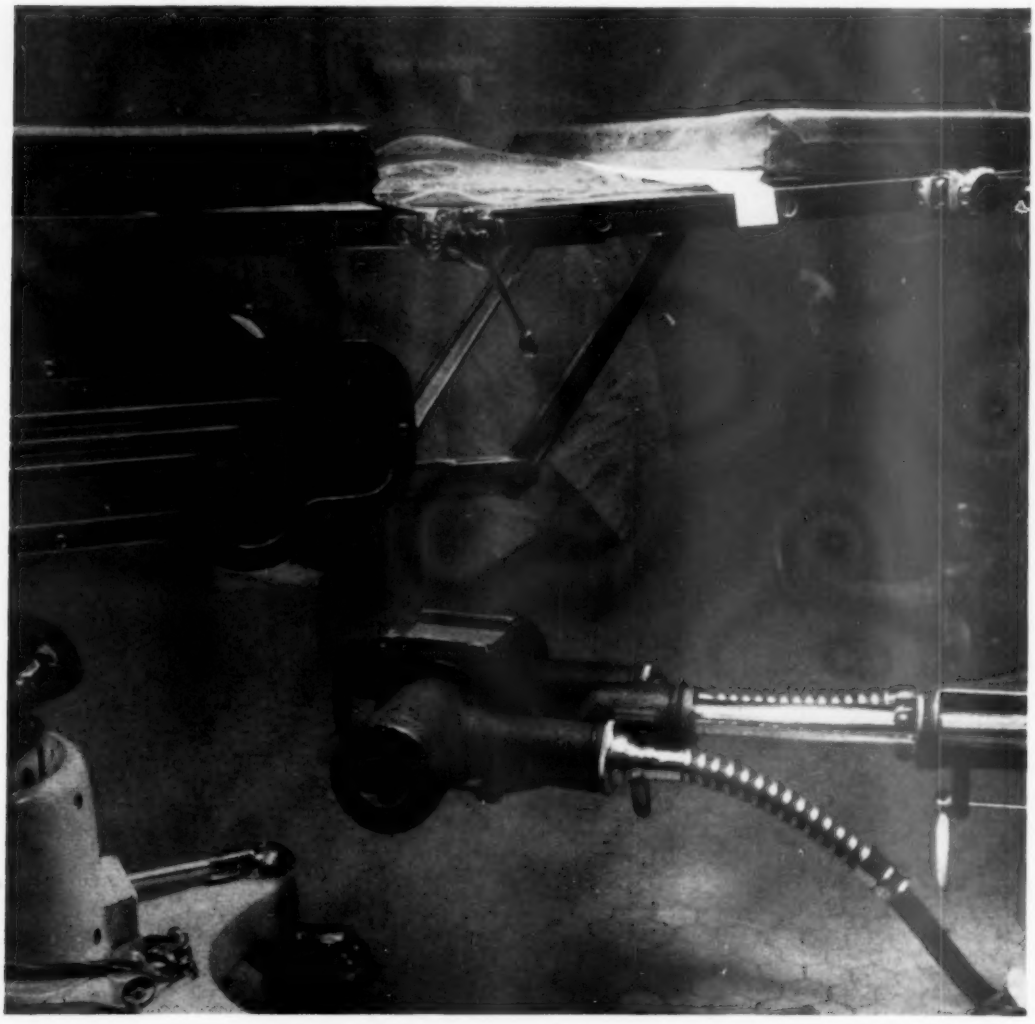

Fig. 2.—The relationship of the operating table and the x-ray machine is shown. The tube is rotated so that the beam is directed upward through the aperture of the operating table.

A simplified operating room cholangiographic technique has been devised which encompasses all the aforementioned desirable factors and offers additional benefits. Many operating room tables* are so constructed that an aperture exists between the foot-

*American Sterilizer Co. operating tables are utilized throughout our hospital.

piece and body of the table. Without such a table the following technique cannot be applied. The table is turned, the foot becomes the head, and the aperture is covered with a radiolucent support of plastic or wood. The patient is positioned with suitable padding so that the right upper quadrant of the abdomen is over the aperture; if desired, the plastic may be molded to give a gall bladder lift, and this latter may be emphasized or made less prominent by the anesthesiologist upon manipulation of the table. A portable x-ray machine is placed beside the head of the patient on the contralateral side from the anesthesia machine. The tube is lowered and placed beneath the table with the head rotated so as to direct the x-ray beam upward through the aperture centering upon the usual anatomic location of the cystic duct-common bile duct junction (Fig. 2). The exposure is thus posterior-anterior.

After the machine has been positioned and a test film made, if desired, the x-ray technician may leave the operating room and the procedure may begin. The technician can be called when needed, and no further manipulation of the heavy radiographic equipment is necessary.

Fig. 3.—Cholangiogram recorded on small intra-abdominal film showing detail of ampullary region and duodenum.

After surgical exploration of the gall bladder area, two exposures are planned (Figs. 3 and 4). The purpose of the first exposure is to study minutely the ampullary region; the purpose of the second exposure is to study the entire duct system. Through the open wound a loaded, thin kidney cassette,* encased in a sterile rubber envelope, is pressed into position over the pancreatic head and duodenal loop and held with a laparotomy pack while the exposure is made. Thus, although the distance from the tube to the cassette is relatively short, the factor of distortion is lessened by the immediate proximity of the terminal duct to the film. The second over-all exposure is recorded upon a 10 by 12 inch

*Picker Kidney Cassette, 3¾ inches by 4¾ inches with par-speed intensifying screens.

film through a grid cassette. This cassette is encased in a sterile pillowcase and placed on the patient's abdomen. Further exposures or a series of exposures may be made as necessary without disruption of the operation.

The contrast material (Diodrast, 35 per cent) is introduced through a No. 7 ureteral catheter secured into either the cystic duct or the common bile duct. Prior to introduction of this medium, an air-free, saline-filled system is established. The long catheter allows for x-radiation safety to the operating team. The initial exposure is made after slowly injecting 10 ml., and the second after 20 ml. has entered, but the amounts used may be varied according to the circumstances.

This technique offers certain advantages. A minute examination of the ampullary region is possible. Heavy radiographic equipment is stationary, and the operative field and drapes are not disturbed. Repeated examinations are readily possible. The long catheter allows for x-radiation safety to the surgical team. Overhead motion, a potential source of bacteriologic contamination, is minimized.

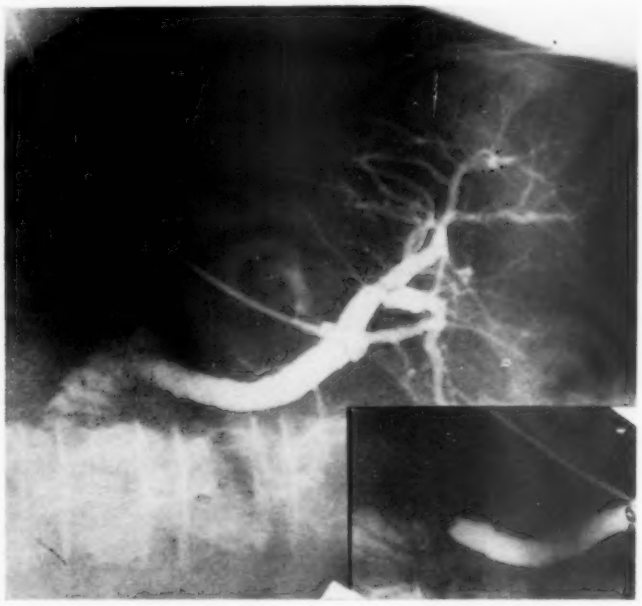

Fig. 4.—Large film and superimposed small (intra-abdominal) film showing detail of terminal common duct. Although the defect noted in the small film suggested the presence of a calculus, none was found on exploration.

CHOLANGIOGRAPHY EXTENDED TO OBSTRUCTIVE JAUNDICE OF THE NEWBORN CHILD

One of the most difficult problems in surgery of the extrahepatic biliary tree is that of obstructive jaundice in the newborn child. For several years we have injected diluted methylene blue solution into any accessible portion of the biliary system as a guide to dissection. In seven consecutive patients we have used methylene blue diluted with Diodrast 35 per cent in order to achieve both direct and radiographic visualization of the ducts. The injection is made through a polyethylene tube or a needle, and the patient is placed in steep Trendelenburg position for visualization of the intrahepatic radicals or in the reverse position for visualization of the distal ductal system.

Cholangiography in these instances aids in determining the presence of communications between the intrahepatic ducts and the major excretory duct. It

is also of aid in selecting the appropriate site of hepatojejunostomy if indicated. Last, it is of aid in distinguishing obstructions in the major duct system due to inspissated bile plugs, partial stenosis, or complete aplasia (Fig. 5).

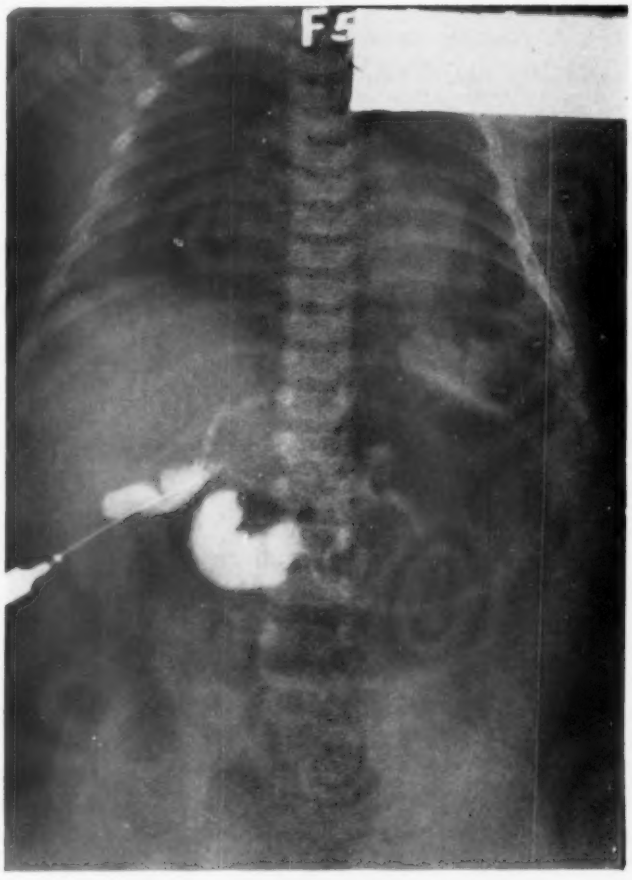

Fig. 5.—Cholangiogram of bile ducts in 3-month-old infant with congenital atresia of the bile ducts.

DISCUSSION

In our hands, operating room cholangiography in over 100 cases has proved it to be of definite value in surgical investigations of the biliary system. Cholangiography is considered an adjunct and not a replacement of other acceptable methods. According to Pribram,[4] residual stones in the common duct after exploration by conventional methods occur in approximately 16 per cent to 25 per cent of cases. We are certain that a number of stones would have been overlooked in our series were it not for radiographic visualization of the duct system during and at the completion of the operation. The presence of one stone within the common duct must make the surgeon wary that others exist, and cholangiography in these instances has been helpful.

To encompass adequately the benefits of the procedure, the surgeon must be familiar with the limitations of the contrast medium and the danger of artifacts. Contrast media which are too dense or in too large amounts are

equally misleading in so far as the detection of stones is concerned. Air bubbles constitute a principal artifact and must not be introduced with the media.

Since July, 1953, the reverse cholangiographic technique described has been used exclusively. This technique appears to be more flexible and free of some technical difficulties inherent in the conventional method.

The extension of the use of operating room cholangiography, particularly to biliary surgery of the newborn child, has appeared rewarding. By the use of this method combined with the methylene blue, the surgeon is afforded a twofold advantage; by visual and radiographic inspection he can assay the anatomic aberrations within the duct system. The cholangiogram provides documentary evidence of the situation and minimizes the possibility of overlooking a remedial condition.

SUMMARY AND CONCLUSIONS

1. Investigation of the factors which influence radiographic visualization of the common duct reveals:

(a) Diodrast 35 per cent is the contrast medium of choice. Higher density media tend to obscure small stones.

(b) Injection of medium in small amounts and without pressure sufficient to distend the duct system provides optimal radiographic visualization, whereas large amounts of the medium and/or distention decreases visualization.

(c) As the size of the common duct stone approaches the size of the duct, the chances of detecting the stone are increased. Packing of stones exerts a similar influence.

(d) Air bubbles are often difficult or impossible to differentiate from calculi; they should be excluded from the system.

(e) The possibility that the density of common duct stones may approach the density of the radiopaque media appears more theoretical than real.

2. A technique of operative cholangiography differing from the conventional method in the following respects is described:

(a) The position of the patient on the operating table is reversed so that the gall bladder area is placed over an aperture between the body and footpiece of the table.

(b) The portable x-ray machine is placed at what is now the head of the table beneath the aperture and directed upward.

(c) Multiple exposures are made, if necessary, on two types of film, a small film placed over the duodenum, and a large film placed over the abdomen.

This technique obviates movement of the x-ray unit during operation, eliminates interference with the operation, decreases the risk of bacterial contamination, and provides films of unusual clarity.

3. The combination of methylene blue dye diluted with Diodrast for direct and cholangiographic visualization of the bile ducts in surgical jaundice of the newborn child has facilitated evaluation and treatment of these difficult problems.

4. Increasing experience has provided greater facility and precision in performing and interpreting the results of cholangiography. In our hands, routine immediate cholangiography has become an important adjunct to the management of patients with biliary tract disease.

Acknowledgment.—The initial clinical trials of this technique were carried out at the Veterans Administration Hospital, Iowa City, and we wish to thank Mr. George Koenig, chief technician of the Department of Radiology. We are also indebted to Mr. R. S. Macy, chief technician, University Hospitals, for his assistance in these studies.

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DISCUSSION

DR. A. DALE CONSOLE (New York, N. Y.).—At the risk of giving the impression that I am trying to get in a commercial, I feel that it might be well to make a few comments about a new contrast medium for cholangiography. This compound, known as Cholografin, is being distributed for investigation by E. R. Squibb & Sons. It is an organic iodine preparation (disodium salt of N,N′-adipyl-bis [3-amino-2:4:6 triiodobenzoic acid]) which has the peculiar property of being excreted in a relatively preferential manner by the liver. Given intravenously, its excretion is rapid, and in well over 80 per cent of patients, there is adequate opacification of the common bile duct, usually the hepatic ducts, and occasionally some of the smaller radicles. Adequate visualization of the bile ducts can be obtained in most patients after cholecystectomy. Adequate concentration of the dye to obtain satisfactory visualization of the biliary ducts usually occurs twenty to thirty minutes after injection, and after approximately one hour the gall bladder also fills. In some patients in whom the usual oral contrast media fail to show visualization of the gall bladder, a cholecystogram can be obtained using this agent.

Many of the advantages of this agent are obvious, and I shall not enumerate them. There need be, for example, no concern about introducing air bubbles and the difficulty of interpretation when this does occur. Since the concentration of the dye is related to the ability of the liver to excrete it, it is possible that it may give a rough index of liver function. While there is no doubt that there will always be some cases which will require operative cholangiography, it appears at this time that the need for this procedure will be greatly reduced.

DR. CHARLES K. KIRBY (Philadelphia, Pa.).—This was certainly a most interesting paper. Several years ago I described an acoustic gallstone detector before this Society. We have found quite a few stones with it and have received letters from a good many people who are finding it successful. It has not worked in as many of the patients as I hoped it might because of the presence in so many cases of soft stones and mud. We are also using operative cholangiography. It is evident that we should use every available means of detecting common duct stones so that we can get all of them out, whenever possible.

FACTORS INFLUENCING NITROGEN METABOLISM IN SURGICAL PATIENTS

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INTRODUCTION

THIS paper is a report of preliminary studies concerned with certain aspects of the metabolic response to operation in patients. An attempt has been made to evaluate some of the factors present in the response to operation by varying the calories, nitrogen, and potassium administered to patients who were subjected to operative procedures of a relatively uniform degree of trauma.

The need for potassium in protein tissue synthesis and amino acid utilization has been demonstrated in experimental animals by Cannon and associates.[5, 6] Corroboration of these results has been presented in studies of patients by Beal, Frost, and Smith.[2] These latter authors also suggested that hypertonic glucose with alcohol was a feasible source of calories in patients when administered intravenously in the period following operation.[1]

Variations in the intake of potassium, nitrogen, and calories were designed to study the influence of these factors individually on the catabolic response to operation.

METHODS

The patients in this series were from the surgical service of the New York Hospital and were operated upon by the resident surgical staff. The patients were transferred to the metabolic ward when they were selected for study and remained in this unit throughout the portion of hospitalization included in the study. Patients who were to undergo cholecystectomy for chronic gall bladder disease or subtotal gastric resection for chronic duodenal ulcer were studied in an effort to have reasonable uniformity of trauma. A control period was obtained prior to operation. The patients were weighed carefully, nude, on the same lever-type scale at the same time each day. Food and water intake was carefully measured and all output collected on a twenty-four-hour basis.

The ingredients of the diets were calculated from standard tables,[3, 17-19] and this information was supplemented where necessary by diet analyses made at the Russell Sage Institute Laboratory at the New York Hospital. Standardized diets were calculated and administered by a dietitian who was a permanent member of the surgical metabolic unit.

Patients undergoing cholecystectomy received an accurately measured diet for at least four days preoperatively. On the operative day and for the first two days postoperatively the intake was maintained by intravenous fluids consisting of 25 per cent glucose and 5 per cent alcohol, 5 per cent fortified protein hydrolysate,* and potassium

Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

*Protein hydrolysate used in this study was Aminisol, made available by the generosity of Abbott Laboratories, North Chicago, Illinois. The protein hydrolysate used in Case A2 was Hyprotigen, supplied through the courtesy of Don Baxter, Inc., Glendale, California.

chloride (see Table I). After the second postoperative day, an oral intake was resumed. Infusions were utilized as supplements to maintain a constant intake of nitrogen, calories, and potassium throughout the postoperative period.

TABLE I. INTAKE OF CHOLECYSTECTOMY PATIENTS, OPERATIVE DAY THROUGH FIFTH POSTOPERATIVE DAY

PATIENT	CAL./KG./24 HR.	N/KG./24 HR. (GM.)	K/KG./24 HR. (MEQ.)	CAL./GM. N
A1	10.7	0	0.6	0
A2	53.3	0.29	2.2	216
A3	16.5	0.38	2.5	44
A4	50.6	0.36	0.8	146

The patients undergoing subtotal gastrectomy were fed in a manner to fit their special requirements. The caloric, nitrogen, and potassium intake are shown in Table II. Patient B1 received a six-feeding gastric diet preoperatively but postoperatively received a diet substantially lower in calories and nitrogen. B2 received no oral feeding until the tenth postoperative day. His caloric and nitrogen requirements were maintained by intravenous route. Patient B3 received an intragastric drip of protein hydrolysate and an oral fat emulsion* as a caloric source. For two days preoperatively and five days postoperatively the patient was given nourishment by the intravenous route only. A progressive gastric regime was then started and the infusions decreased so that the intake per day remained constant. Patient B4 received a six-feeding gastric diet preoperatively after relief of pyloric obstruction with an intragastric drip. Postoperatively nutriment was supplied entirely by the intravenous route until the eighth day.

TABLE II. INTAKE OF SUBTOTAL GASTRECTOMY PATIENTS, OPERATIVE DAY THROUGH EIGHTH POSTOPERATIVE DAY

PATIENT	CAL./KG./24 HR.	N/KG./24 HR. (GM.)	K/KG./24 HR. (MEQ.)	CAL./GM. N
B1	7.2	0.02	0.7	32
B2	40.9	0.49	1.9	84
B3	33.0	0.27	2.1	122
B4	33.8	0.17	1.3	194

All patients were kept in water and electrolyte balance from day to day and maintained adequate urinary outputs throughout the study. Serum electrolyte levels were determined frequently and were corrected when necessary.

Urine, stools, and gastric drainages, when present, were collected from 9:00 A.M. to 9:00 A.M. Prior to the onset of the study the patients were given cathartics or enemas, and the stool obtained discarded. Surgical dressings were leached out and nitrogen and electrolytes determined on the fluid.

All analyses and determinations reported herein were made in the laboratory for surgical research. Sodium and potassium values were determined using the Barclay flame photometer and the flame photometer attachment of the Beckman D.U. spectrophotometer. The micro-Kjeldahl technique was used for all nitrogen determinations, and total reducing sugar in the urine was determined by the modified Folin-Wu method.[8, 10-12] Plasma protein values were determined by micro-Kjeldahl, and the fractions were separated by sodium sulfate precipitation.

In patient B4, who developed hematuria, urinary protein was determined by a sulfosalicylic acid turbidimetric method,[4] and the nitrogen derived from this protein was subtracted from the total nitrogen output as representing nonmetabolic loss of nitrogen.

*The oral fat emulsion, Ediol, was supplied through the courtesy of Schenley Laboratories, Inc., Lawrenceburg, Indiana.

The balance studies are summarized by the technique of Reifenstein and associates[15] and later by Moore.[14]

The lean tissue values charted in Figs. 6 and 11 represent the nitrogen balance multiplied by a factor of 30.[14]

RESULTS

A balance study in a patient preceding operation is presented to demonstrate the relation between nitrogen retention and potassium intake (Fig. 1). This patient was considered to be nitrogen deficient because of the short period of inadequate intake resulting from an obstructing duodenal ulcer prior to the period of study. In the initial phase of the study, protein hydrolysate was administered by an indwelling intragastric tube, but additional potassium was not supplied. In the second phase, the daily nitrogen and relatively low caloric intake was essentially unchanged, but additional potassium was placed in the protein hydrolysate so that the daily potassium content was increased from 30 meq. to an average of 100 meq. The prompt appearance of a positive nitrogen balance is evident and confirms previous experiments conducted along similar lines.[2]

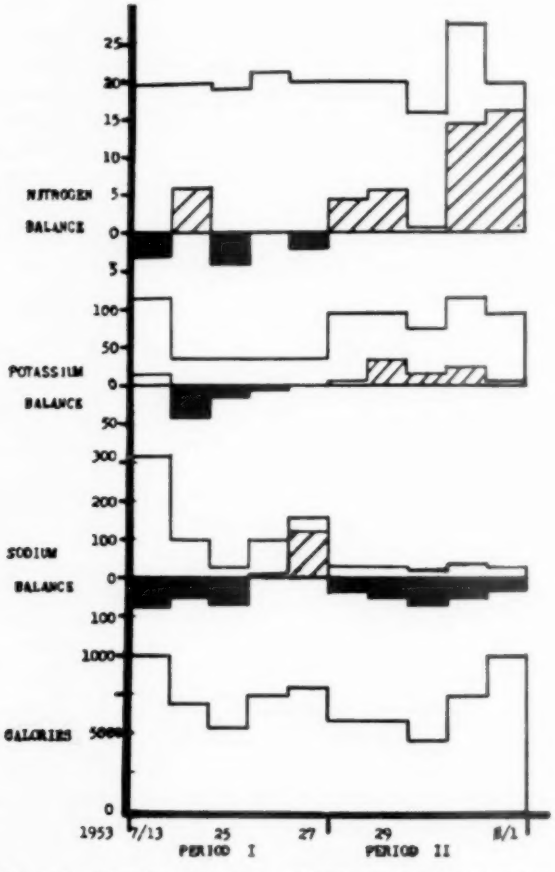

Fig. 1.—NYH #605 348, 46-year-old man. Chronic duodenal ulcer with obstruction.

The results of the studies of the patients undergoing operative procedures are presented in two sections because of the variation in the extent of trauma. The importance of considering the degree of trauma in the response pattern has been discussed by Moore.[14]

Response to Cholecystectomy (Figs. 2, 3, 4, 5, and 6).—The four patients who were subjected to cholecystectomy were well-nourished and well-developed females who had been ingesting adequate low-fat diets prior to admission. The operative procedures were of approximately the same duration and were performed by surgeons of comparable experience on the resident staff. The course following operation in one patient (Case A2, Fig. 3) was complicated on the fourth day after operation by an elevation of temperature to 38.5° C., which clinically was considered due to either a hematoma or retroperitoneal cellulitis in the right flank secondary to mobilization of the right colon performed to accomplish an incidental appendectomy. The other three patients recovered uneventfully.

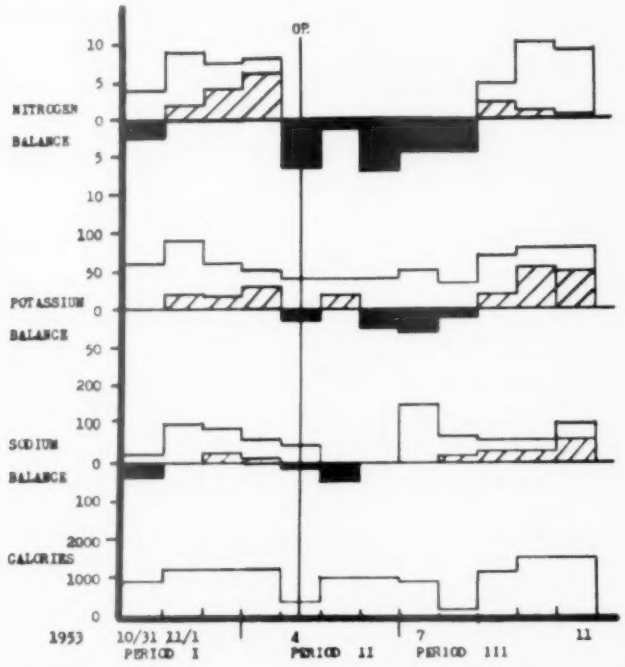

Fig. 2.—Case A1, NYH #565 529, 62-year-old woman. Chronic cholecystitis with cholelithiasis. Operation: cholecystectomy and appendectomy.

One patient is presented as a control study (Case A1, Fig. 2). The parenteral alimentation in this patient was designed to represent that usually employed, and additional calories and nitrogen were not supplied. The response pattern is typical and has been well described elsewhere.[14] The intake of the remaining three patients had certain variations in the form of additional nitrogen, potassium, and calories in the intravenous fluids administered before, during, and following operation, which are summarized in Table I. The results are discussed under separate categories as follows:

1. *Nitrogen:* Negative nitrogen balance occurred promptly on the day of operation in the control patient (Fig. 2), who did not receive intravenous protein hydrolysate in the period following operation. Negative balance persisted until the fifth day after operation. Each of the other three patients received nitrogen as protein hydrolysate beginning with the operative period, and it is interesting to note that negative balance was delayed until the first or second day after operation. The pattern of the negative balance in Case A2 (Fig. 3) is difficult to interpret because of the complicating fever on the fourth

postoperative day. The second episode of negative balance is felt to represent largely the result of a second superimposed stress stimulus. In Case A3 (Fig. 4), of a patient who received 0.38 Gm. per kilogram daily of nitrogen, negative nitrogen balance persisted for only three days. Case A4 (Fig. 5), of a patient who was given 0.36 Gm. per kilogram of nitrogen daily, presented a somewhat different pattern of response. The period of negative balance began on the first postoperative day and lasted until the sixth day. The fourth day showed the greatest loss of nitrogen.

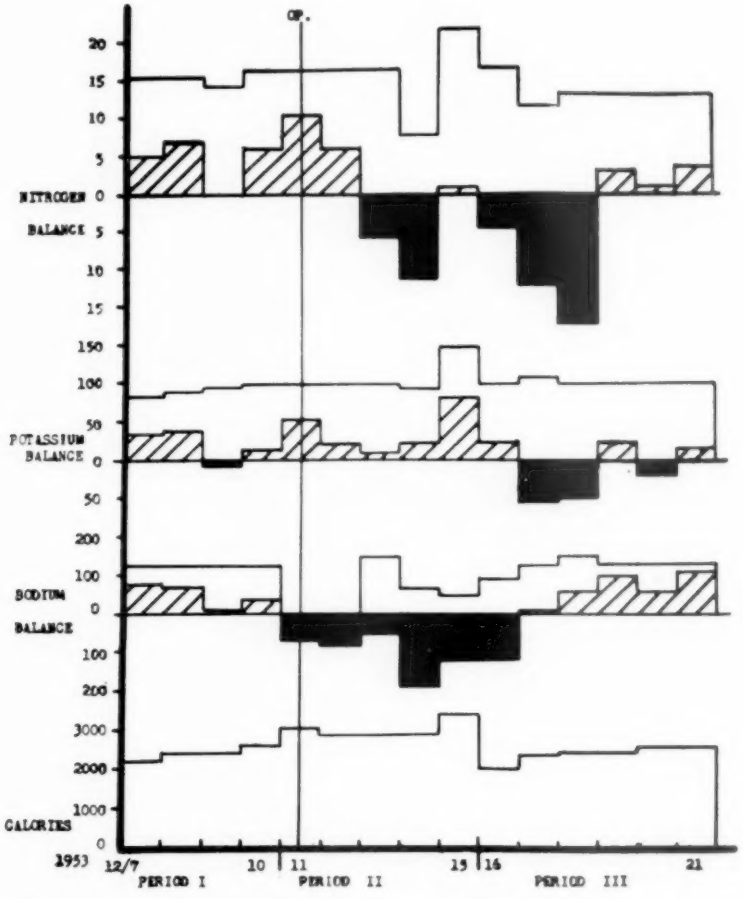

Fig. 3.—Case A2, NYH #671 968, 40-year-old woman. Chronic cholecystitis with cholelithiasis. Operation: cholecystectomy and appendectomy.

2. *Potassium:* The usual negative balance of potassium on the day of operation was found in the patient who served for the control study (Case A1). The amounts of potassium contained in infusions given during the period following operation were those customarily administered by the resident staff to prevent potassium deficiency (40 meq. per day). Two patients in the group received 100 meq. or more of potassium daily (A2, A3) and remained in positive potassium balance during the first five postoperative days, including the day of operation. There were no significant alterations of the serum potassium levels. There does not appear to be any correlation between potassium and nitrogen balance in these patients with the degree of trauma represented by cholecystectomy.

3. *Sodium:* The sodium balance does not appear to be remarkable in this group. The usual sodium-retaining tendency may be obscured in some instances by preoperative salt loads (Fig. 3) and by low intake (Fig. 4) in association with the high fluid intake and urinary output (more than 2,000 c.c. urine volume daily).

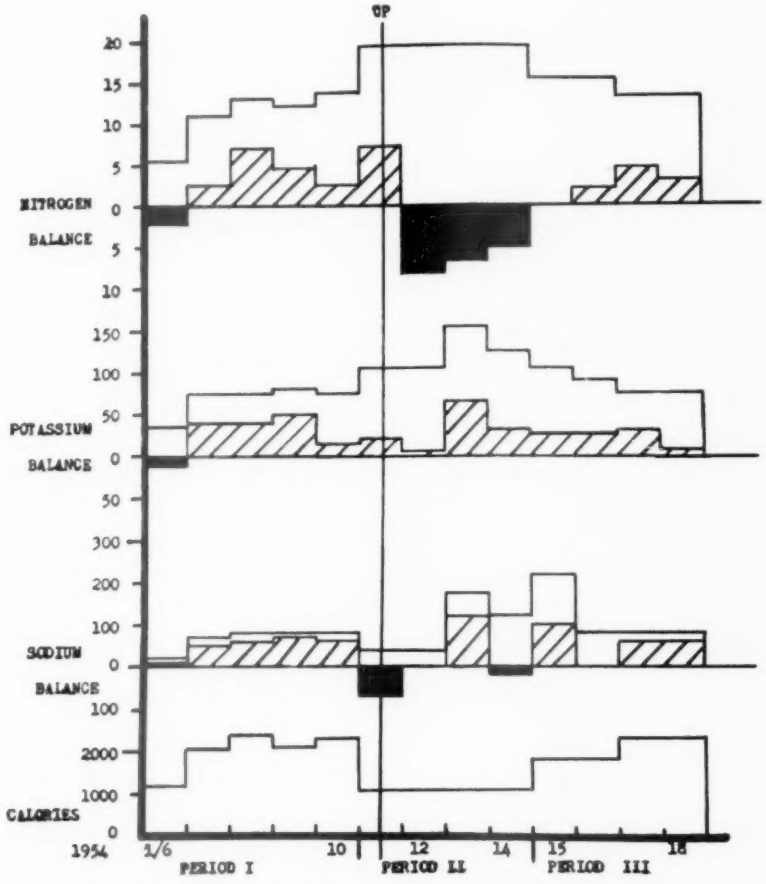

Fig. 4.—Case A3, NYH #92 283, 44-year-old woman. Chronic cholecystitis with cholelithiasis. Operation: cholecystectomy.

4. *Relation of caloric intake to lean tissue change:* The patient acting as a control (A1) received only the caloric intake usually administered to patients in the immediate postoperative period before oral feeding is tolerated. A second patient (A3) also had a low caloric intake, but was given nitrogen and potassium. Two of the patients (A2, A4) received infusions of 25 per cent glucose and 5 per cent alcohol in order to maintain a high caloric intake. The retention of glucose was satisfactory and resembled the experience previously presented when these solutions were used in postoperative patients. It should be noted that, in the two patients receiving high caloric intake, the calorie to nitrogen intake ratio exceeded that of the average general diet (120 calories: 1 Gm. nitrogen).

The lean wet tissue changes in these four patients have been calculated and charted for the immediate postoperative period. It appears that the lean wet tissue loss is diminished in those patients who received nitrogen (protein hydrolysate) following operation. In addition, the two patients who received

an increased caloric intake appear to have lost a smaller amount of lean wet tissue. The correlation of potassium intake with lean wet tissue changes is uncertain because the variation in potassium administration was insufficient in this small series.

Response to Subtotal Gastrectomy (Figs. 7, 8, 9, 10, and 11).—The patients comprising this group were all men. The extent of the operative procedures was reasonably uniform, and the duration of anesthesia was comparable. However, the status of the patients differed in that one was markedly depleted (Case B2, Fig. 8).

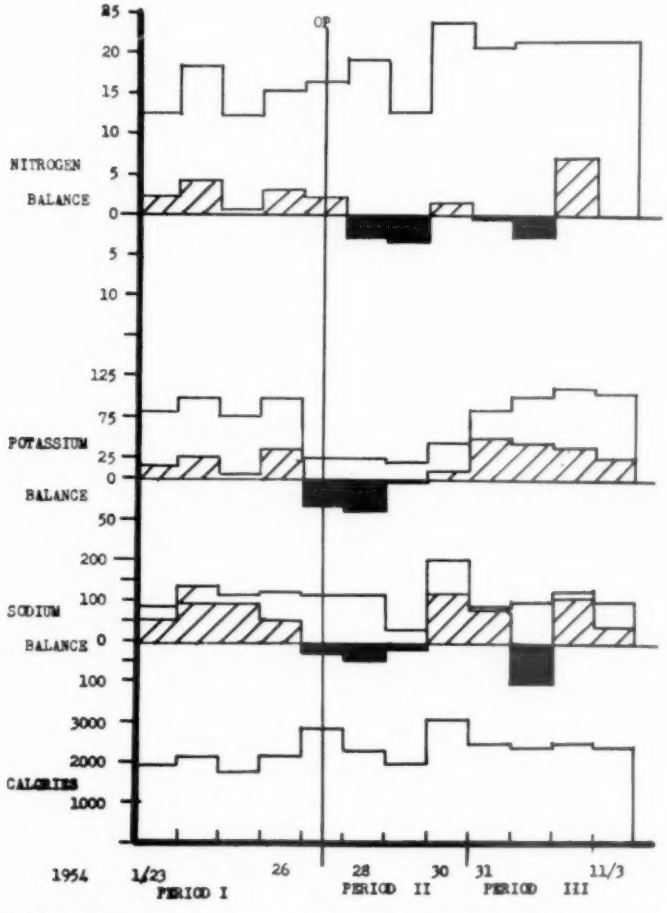

Fig. 5.—Case A4, NYH #647 015, 22-year-old woman. Chronic cholecystitis with cholelithiasis. Operation: cholecystectomy and appendectomy.

The patient who was studied as a control (Case B1, Fig. 7) received solutions of 5 per cent glucose in water or saline solution as customarily ordered by the resident staff, beginning on the day of operation. Potassium was added to the infusions in amounts usually considered sufficient to prevent potassium deficiency. Nitrogen was not given until oral intake was resumed on the sixth day after operation.

The other three patients (Figs. 8, 9, and 10) received intravenous alimentation designed to increase potassium, nitrogen, and caloric intake beginning with the operative period. This consisted of 6 per cent protein hydrolysate and 25 per cent glucose with 5 per cent alcohol. All solutions contained additional quantities of potassium. This is summarized in Table II.

The features of the metabolic response are discussed in the following sections:

1. *Nitrogen:* The control patient (Case B1, Fig. 7) had the onset of negative nitrogen balance on the day of operation and developed nitrogen equilibrium on the sixth day when nitrogen intake was resumed with oral feedings. The most marked negative nitrogen balance occurred two days after operation. The patient who was markedly depleted (Case B2) was maintained by intravenous alimentation without oral intake for twenty-two days before operation. His response to operation was characterized by predominantly positive nitrogen balance, with three days of negative balance interspersed throughout the immediate postoperative period. His course was accompanied by a progressive increase in serum protein levels. The third patient (Case B3) received an average of 13.8 Gm. of nitrogen daily (0.27 Gm. per kilogram) for six days beginning the day of operation. Negative nitrogen balance became manifest the day following operation, and positive balance was attained on the sixth postoperative day. The fourth patient (Case B4, Fig. 10) represents an excessive response to operation.[14] Negative nitrogen balance occurred the day of operation and continued throughout the period of study, although he received an average daily intake of 13.5 Gm. of nitrogen (0.17 Gm. per kilogram). The patient was a tense, apprehensive individual whose course was marked by unusual slowness to resume oral feedings and marked anxiety over urinary retention and hematuria from catheterization.

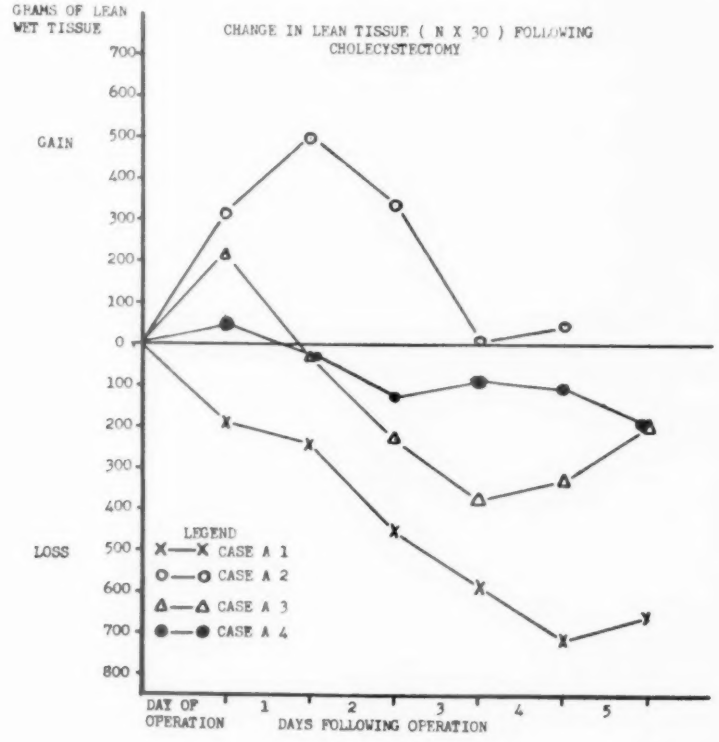

Fig. 6.

2. *Potassium:* With the degree of trauma represented by subtotal gastrectomy, the administration of as much as 2.1 meq. per kilogram per day did not result in positive potassium balance in the immediate postoperative period in any instance. The balance pattern did not seem to be significantly dif-

ferent in the four patients although two who received more than 90 meq. of potassium the day of operation demonstrated positive potassium balance for that twenty-four-hour period. The depleted patient was noted to return to positive balance earlier than the other three.

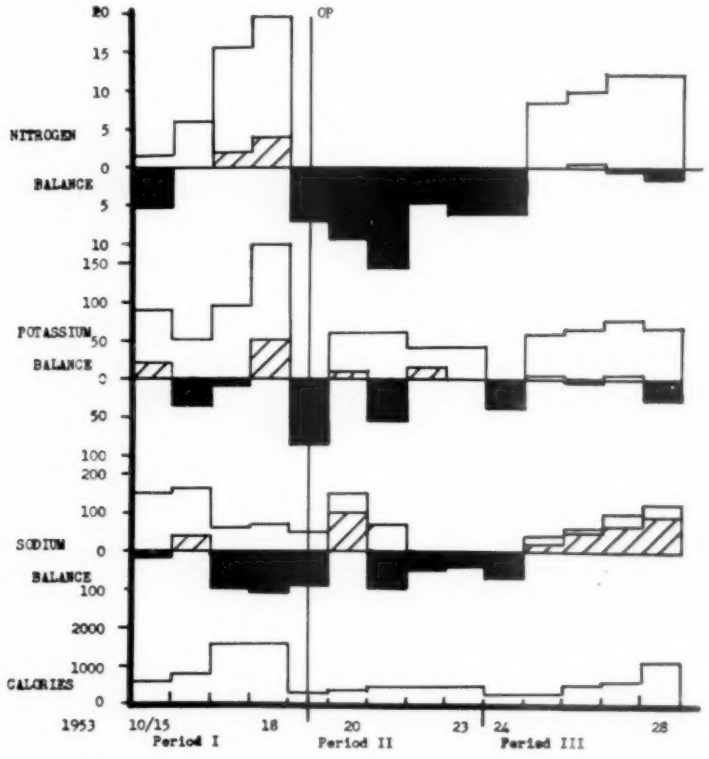

Fig. 7.—Case B1, NYH #129 633, 56-year-old man. Duodenal ulcer. Operation: subtotal gastrectomy.

3. *Relation of caloric intake to lean tissue change:* The caloric intake in this group was varied and is summarized in Table II. On a body-weight basis, two patients (Cases B3 and B4) were supplied with calories within the range of basal requirements but were maintained on a high calorie:nitrogen ratio (Table II). Changes in lean wet tissue for this group are presented in Fig. 11. The protein-depleted patient (Case B2), who received 40.9 calories per kilogram per day and 0.49 Gm. nitrogen per kilogram per day following operation, demonstrated a slight gain in lean wet tissue in the postoperative period which, however, represented a much slower rate of gain than had been present in the period preceding operation. The remaining three patients lost lean tissue in the same period after operation. Lean tissue loss in the patient in Case B3, who received 33 calories per kilogram per day and 0.27 Gm. nitrogen per kilogram per day, appeared to be significantly less than that in the control case, in which nitrogen was not administered. The duration of the period of lean tissue loss was comparable, but the calculated total loss was diminished for the patient who recived nitrogen.

DISCUSSION

The pattern of the catabolic response to operation is now a familiar one. The correlation of these changes with adrenocortical activity has done much

to enhance our understanding of the physiologic changes involved. It is known that the catabolic response to trauma such as operative intervention is a strong biologic reaction and appears to be obligatory in that the loss of nitrogen is not changed significantly by the administration of small quantities of nitrogen. However, it has not been established that it is a desirable response for the organism. Furthermore, to state that administered nitrogen is

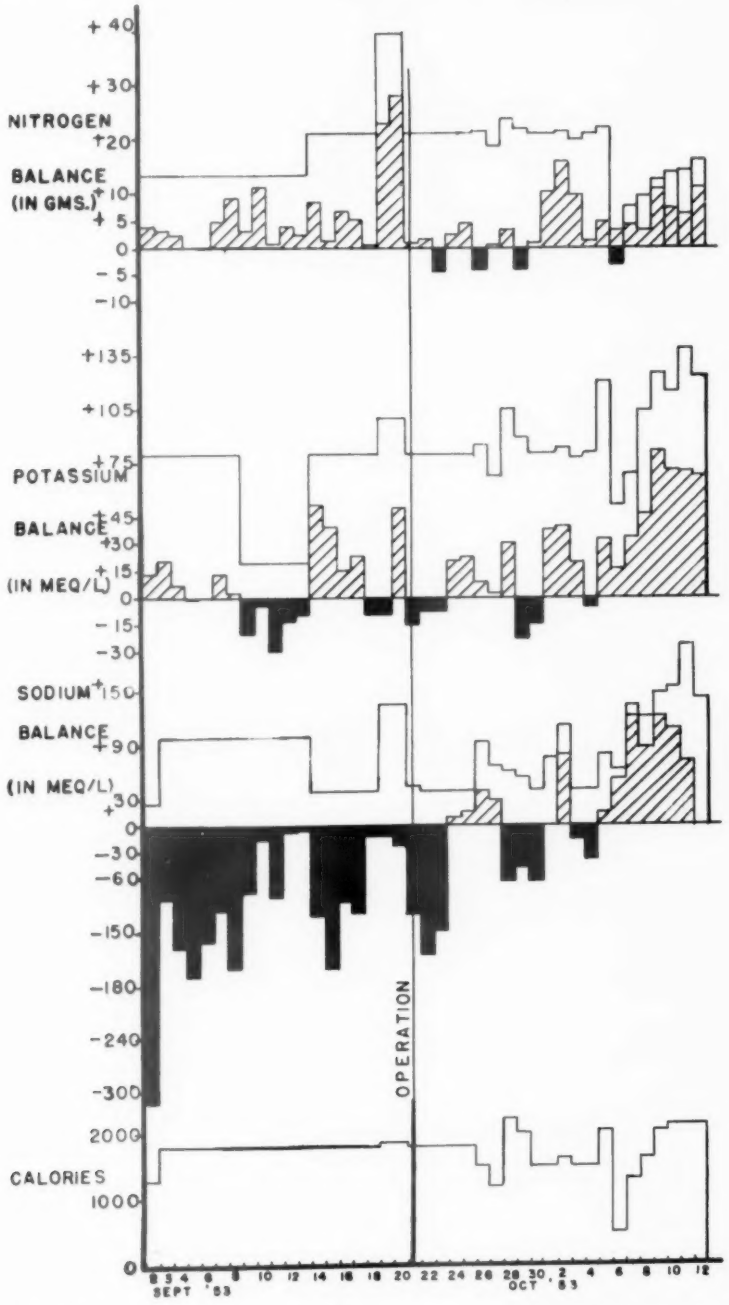

Fig. 8.—Case B2, NYH #216 507, 44-year-old man. Postoperative gastroileostomy. Operation: subtotal gastrectomy.

without benefit to the organism following operation implies either that the body tissues are totally unable to use it or that it is lost too rapidly during the stress period.

Evidence shows that exogenous nitrogen can be utilized following injury. Amino acids tagged with radioactive isotopes have been found to be incorporated in the tissues of experimental animals after acute injury.[13] This indicates that the anabolic phase is not entirely absent following trauma, although the catabolic phase does predominate. Evidence has been presented from studies in man that the loss of nitrogen in the period following surgery can be diminished by increasing the caloric and nitrogen intake.[7, 16, 20] This suggests that the catabolic loss of body tissue is related to insufficient administration of energy and protein.

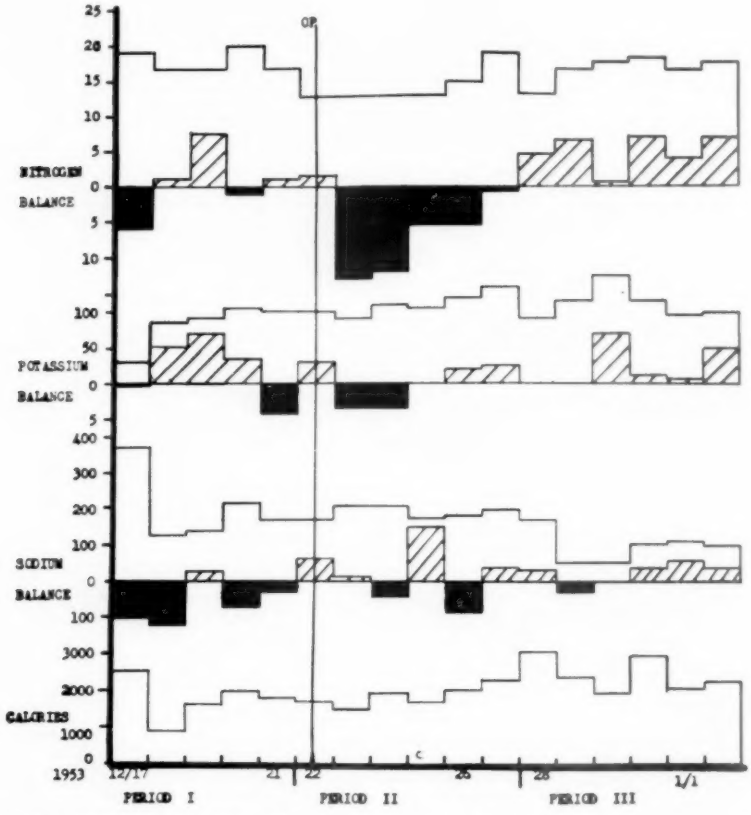

Fig. 9.—Case B3, NYH #672 168, 39-year-old man. Duodenal ulcer. Operation: subtotal gastrectomy.

The present study appears to support this contention. Of the two cholecystectomy patients who received both a high calorie and a high nitrogen intake throughout the operative period, one remained in nitrogen balance, and the catabolic phase in the other was smaller than that of the control patient in the group. Admittedly this is a small group of patients to allow such conclusions, but it is felt that the similarity of the trauma in the four patients permits making a preliminary statement on this subject.

There is no doubt that the magnitude of the operation or severity of the trauma will greatly affect the chances of reversing the catabolic phase following trauma. This is apparent in the second group of patients in the present series, those undergoing gastrectomy. The degree of stress, as well as the preoperative nutritional state, differed sufficiently in these patients so that it is impossible to prove that the high caloric and nitrogen intake of the patients who received it at operation affected the catabolic response. Clearly, a longer series is required.

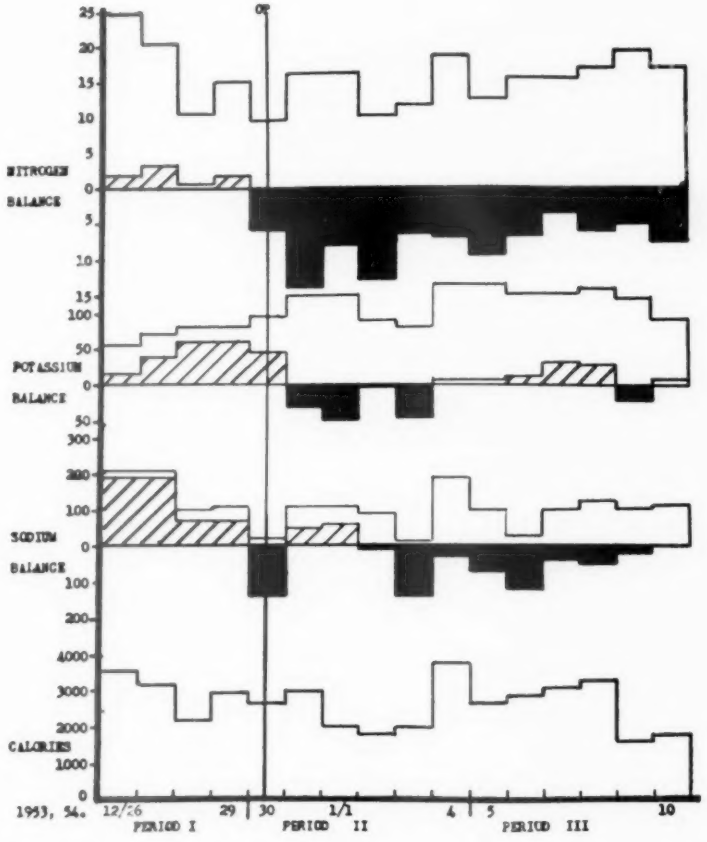

Fig. 10.—Case B4, NYH #669 103, 39-year-old man. Duodenal ulcer. Operation: subtotal gastrectomy.

The severity of trauma also influenced the potassium balance in the present series. This electrolyte does not appear to be completely under neuroendocrine control although its pattern of excretion is strongly under the influence of adrenocortical activity.[9] When trauma was of lesser degree, as represented by cholecystectomy, a significant increase in intake was associated with a positive potassium balance, even in the presence of a negative nitrogen balance. With more trauma, as in gastrectomy, loss of potassium was not prevented by increased administration.

Supplying nitrogen and calories during stress should affect a sparing action on the patient's lean tissue. Although this may not be of practical

importance in many surgical patients, it should be considered in depleted patients who require immediate surgical intervention, or in patients who are unable to take oral feedings for a protracted time postoperatively. A long catabolic phase postoperatively cannot be considered desirable or harmless. Further study of means to minimize the catabolic phase seems therefore worth while. However, many technical difficulties are now present when attempts are made to supply the postoperative patient with the necessary nutrients with fluids that are currently available. Basal caloric and nitrogen requirements are 30 to 35 calories per kilogram per day and 0.16 Gm. per kilogram per day, respectively. When this material must be injected intravenously, it amounts to 3 L or more of solution, which may not be feasible in some patients.

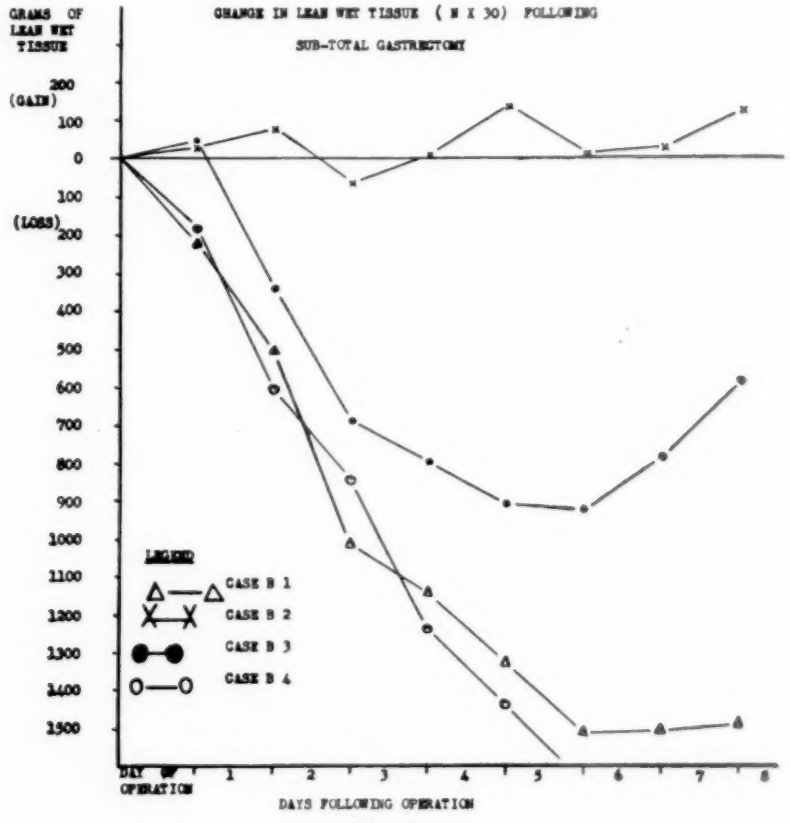

Fig. 11.

It is of interest that the patients in this series, with one exception, who received increased parenteral nitrogen beginning with the operative day did not develop negative nitrogen balance until the first postoperative day. The patients in this series, as in other reports, who did not receive nitrogen uniformly developed a strongly negative nitrogen balance on the day of operation.[14] It would appear from this observation that much of the loss of nitrogen on this day reflects the "starvation state" that begins the night before major operations. The catabolic response probably is not manifest until the first day after operation.

SUMMARY

Balance studies have been presented from two groups of patients who were subjected to operative procedures of two different degrees of stress. Variations in caloric, nitrogen, and potassium intake were utilized to evaluate their influence on the catabolic response to operation. From these preliminary studies it would appear that loss of lean tissue can be diminished by markedly increasing the intake of these factors. The effect is related to the previous nutritional state of the patient and to the degree of trauma.

CASE REPORT SUMMARIES

CASE 1.—This 46-year-old white man (NYH #605 348) was admitted July 20, 1953, with signs and symptoms of pyloric obstruction of four days' duration. The patient had been treated in the outpatient department for the preceding seven months after a duodenal ulcer had been detected by gastrointestinal roentgenograms. Physical examination was unremarkable except for moderate obesity. Routine laboratory tests were negative except for a leukocytosis of 13,600. *Course:* Following admission the patient was transferred to the metabolic unit, and a continual intragastric grip of protein hydrolysate was instituted. Periodic gastric aspiration was performed to determine the amount of gastric retention. The period of study was terminated twelve days after admission, and the patient was then permitted to take a six-feeding gastric diet. Subtotal gastric resection was performed on the eighteenth hospital day, and recovery was uneventful.

CASE A1.—A 62-year-old white woman (NYH #565 529) was admitted Oct. 1, 1953, with symptoms of gall bladder disease of three years' duration. Subtotal thyroidectomy for toxic nodular goiter had been performed three years previously with good result. The present admission had been precipitated by an attack of biliary colic four days earlier. Examination was unremarkable except for moderate obesity. There was no jaundice. Laboratory findings were within normal limits. A cholecystogram demonstrated cholelithiasis. *Course:* The patient was transferred to the metabolic unit, where a measured diet was given and balance studies, as recorded in Fig. 2, were instituted. Cholecystectomy and appendectomy were performed six days after admission. The pathologic report was chronic cholecystitis, cholelithiasis, and vermiform appendix. Recovery was uneventful, and the patient was discharged eight days after operation.

CASE A2.—This 40-year-old white woman (NYH #671 968) was admitted Dec. 2, 1953, with gall bladder symptoms of twenty years' duration. An acute episode of pain, nausea, and vomiting occurred ten days prior to admission and had subsided. The only pertinent physical finding was moderate tenderness in the right upper quadrant on deep abdominal palpation. Laboratory data were within normal limits except for leukocytosis of 12,600. Cholecystography demonstrated cholelithiasis. *Course:* Five days after admission the patient was transferred to the metabolic unit, where balance studies were begun. She received a measured low-fat diet. Five days later cholecystectomy and appendectomy were performed. Chronic cholecystitis with cholelithiasis and vermiform appendix was reported by the pathologist. The balance studies were continued during the period after operation, and the patient was discharged eleven days after operation.

CASE A3.—This 44-year-old white woman (NYH #92 283) was admitted Jan. 5, 1954, because of symptoms of gall bladder disease of four years' duration, which had been increasing in severity. A cholecystogram had demonstrated cholelithiasis. Physical examination was unremarkable. Laboratory findings were within normal limits. *Course:* The patient was admitted to the metabolic unit, and balance studies were instituted. Five days after admission cholecystectomy was performed. Balance studies were continued after operation. The patient was discharged on the eighth day after operation.

CASE A4.—A 22-year-old white woman (NYH #647 015) was admitted Jan. 22, 1954, with attacks of postprandial abdominal distress of seven months' duration, occasionally associated with vomiting, which had become more severe in the month before admission. Physical examination was unremarkable. Pertinent laboratory findings revealed cholelithiasis by cholecystogram. *Course:* After admission the patient was transferred to the metabolic unit and received a measured low-fat diet. On the fifth hospital day the patient was subjected to cholecystectomy and incidental appendectomy. Convalescence was uneventful, and she was discharged on the seventh postoperative day.

CASE B1.—This 56-year-old white man (NYH #129 633) was admitted Oct. 3, 1953, because of epigastric pain and intermittent nausea and vomiting of one month's duration. The patient had ulcer symptoms beginning in 1939, and a duodenal ulcer was demonstrated in 1950 when partial pyloric obstruction and hemorrhage occurred. Examination demonstrated slight epigastric tenderness and was otherwise unremarkable. Laboratory findings were within normal limits except for a leukocytosis of 17,700. *Course:* The patient was admitted to the metabolic unit and all intake and output were measured for metabolic balance studies. Sixteen days after admission subtotal gastric resection was performed. The pathologic diagnosis was chronic duodenal ulcer with obstruction. Balance studies were continued until the time of discharge on the tenth day following operation.

CASE B2.—A 44-year-old white man (NYH #216 507) was admitted Aug. 30, 1953, complaining of diarrhea and marked weight loss following an operation for peptic ulcer performed one year earlier at another hospital. Ulcer symptoms dated back fifteen years, and roentgenograms had demonstrated a duodenal ulcer. Operative intervention had been undertaken following an acute exacerbation of symptoms. Diarrhea became apparent one week after operation and persisted. Eight to more than thirty stools a day were reported by the patient, who frequently detected undigested food in the stools. A 70-pound weight loss was recorded. Edema of the lower extremities was noted three months prior to admission, which progressively increased until edema extended to the iliac crests. Two transfusions of whole blood were administered elsewhere during this period because of "anemia." Roentgenograms of the gastrointestinal tract demonstrated that an anastomosis had been performed between the remaining segment of stomach and the ileum approximately 30 cm. from the ileocecal valve. Physical examination disclosed the following pertinent findings: The patient was an emaciated, chronically ill white man with dry skin. Multiple friable fissures were present at the corners of the mouth; the abdomen was scaphoid; marked edema of the lower extremities was present and extended upward including the lower abdomen and genitals. Laboratory findings included the following: Hemoglobin 11 Gm., hematocrit 31 per cent, white blood count 2,500 with a normal differential; prothrombin time was prolonged; serum sodium, potassium, and chlorides were within normal limits; serum proteins 4.0 Gm., albumin 1.8 Gm., and globulin 2.2 Gm. Stools were intermittently positive for occult blood. An electrocardiogram showed changes suggestive of electrolyte imbalance. *Course:* The patient was transferred to the metabolic unit, and balance studies were begun. Oral intake was withheld and intravenous alimentation begun. These measures are summarized in Fig. 8. Twenty-two days after admission the gastroileostomy was dismantled, and a gastrojejunostomy was established. Balance studies were continued. The postoperative course was complicated only by a brief period of ileus for three days beginning on the ninth day after operation. The patient was discharged twenty-three days after operation. Pathologic examination of the segment of stomach removed failed to demonstrate unusual findings.

CASE B3.—A 30-year-old white man (NYH #672 168) was admitted Dec. 8, 1953, with pyloric obstruction due to a chronic duodenal ulcer, which had been symptomatic for about three years. Increased ulcer pain, nausea, and vomiting had begun two weeks before the patient was admitted and had been accompanied by a loss of 16 pounds of weight. Positive physical findings: thyroid diffusely enlarged about twice normal size without bruit or

tracheal displacement; abdomen: moderate epigastric tenderness. Laboratory data were pertinent as follows: serum sodium 136 meq. per liter, CO_2 29 mm. per liter; serum protein 5.1 Gm. with albumin 3.6 and globulin 1.5 *Course:* Following admission, gastric aspiration was continued for thirty-six hours and was replaced by a continual intragastric drip by means of the nasogastric tube. The contents of the solutions administered are recorded in Fig. 9. Thirteen days after admission, subdiaphragmatic vagotomy, antrectomy, and gastrojejunostomy were performed. Studies were continued in the period after operation. The patient recovered without complication and was discharged twelve days after operation.

CASE B4.—A 39-year-old white man (NYH #699 103) was admitted Dec. 17, 1953, because of an exacerbation of ulcer symptoms from a duodenal ulcer which had been present for at least ten years. The ulcer had been recently demonstrated by roentgenograms. Physical examination was unremarkable except for tenderness in the epigastrium. Laboratory findings were within normal limits. *Course:* Following admission, the patient received standard ulcer therapy with hourly feedings. Five days after admission he was transferred to the metabolic unit for study. A small-caliber nasogastric tube was inserted, and continuous feedings were begun by this route, a summary of which therapy is presented in Fig. 10. On the thirteenth hospital day, a subtotal gastric resection was performed. Studies were continued after operation. Recovery was complicated by transient urinary retention and hematuria secondary to catheterization. He was discharged twelve days after operation.

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DISCUSSION

DR. HENRY THOMAS RANDALL (New York, N. Y.).—Most of these studies that have been carried out represent a great deal of time and effort on the part of the investigators, as those of us who have been connected with them well know.

I think that as these studies go on, and more and more groups report their results, it becomes fairly evident that one can very definitely reduce the amount of nitrogen loss which any patient has in the immediate postoperative period by the administration of both large amounts of nitrogen and a considerable amount of calories. There is a great deal of effort involved in doing it and certainly, at least with the preparations which are available at the present time, either large volumes of fluid are required or extremely hypertonic materials must be administered. Hypertonic solutions have to be administered at an extremely slow rate or through a polyethylene catheter into a large vessel with a high rate of flow.

Like many arguments, I suppose, the question will eventually come down to what represents the practical use of high nitrogen, high potassium, and high caloric intake in the hands of the practicing surgeon.

Dr. Beal and Dr. Cornell's work is of interest to me because of the fact that they were able to administer as much as 100 to 150 meq. of potassium a day. I have always thought that the administration of potassium in the first twenty-four hours following surgery was a little dangerous because you could not always predict what the renal output of the patient was going to be and that, therefore, there was a possibility of getting into difficulty with elevation of the serum potassium level. I am sure, however, that if potassium in this amount is administered with a high caloric intake, it is less dangerous than if administered merely by itself.

I feel that the patients who really need calories and nitrogen are rather different from the relatively well patients whom most of us start out to study. The depleted patients are the ones who are certainly less likely to have any major, if you will, large alarm response and nitrogen loss in the postoperative period.

I would like to ask two questions. One of them is: I wonder if Dr. Cornell would describe for us the types of solutions and the method of administration which he used in order to accomplish these, almost positive balances or positive balances in some instances. Second, with the administration of this much potassium, I would like to ask him what effect there was on the plasma bicarbonate-combining power. It has been demonstrated by our friends, the physiologists, that large amounts of potassium chloride administration tend to have a depressing effect on the bicarbonate by causing an increased excretion of bicarbonate by the kidneys. I wonder whether he observed this, and if so, what happened?

DR. JAMES DANIEL HARDY (Memphis, Tenn.).—I felt certain that both of the previous speakers were about to mention what Cannon and his associates have recently shown, namely, that an adequate amount of potassium is necessary for the fabrication of protein. This is of particular interest in that, as the years go by, it is more and more apparent that electrolytes are not present merely to establish osmolar concentration and to regulate acid-base balance, but that they have important additional functions in the general metabolism. Leninger has pointed out that most of the bulk electrolytes, such as sodium and potassium, play a very essential role in the integrity of various enzyme systems which regulate cytochemical processes.

DR. WILLIAM M. SHINGLETON (Durham, N. C.).—May I make one comment, please. I would like to report briefly on some recent work that we are doing on intravenous fat emulsion as a way of supplying calories in the early postoperative period and in what manner calories supplied in this way might influence the negative nitrogen balance. We have completed these studies in only a few cases. In some three patients up to date, we have found that calories supplied by way of intravenous fat are quite effective in decreasing the negativity of the nitrogen balance.

DR. FRANCIS D. MOORE (Boston, Mass.).—I would just like to ask the speaker how he treated Patient B4 both before and after operation. The reason I wanted to ask about Patient B4 was that he seemed to lose as much nitrogen as anyone and was regarded as being a hyperreactor. Also, I think it is important to realize that the work described, which is extremely careful, very interesting work, is based on a fairly small number of patients. Without many patients treated the same way (and the standard deviation of differences in daily nitrogen excretion being great), one must be extremely hesitant in drawing conclusions from small differences.

I think Dr. Randall put his finger on it in saying we have two problems. One is a theoretical one and of great interest; namely, what is this all about—this loss of nitrogen? The other is a practical one. We all agree that there is no use dumping a lot of nitrogen into early postoperative patients when they are perfectly healthy, and I do not think the speaker meant to imply that. The theoretical implication of their work is great, but I feel very reserved about it because of the relatively few number of instances.

In regard to Dr. Shingleton's comment, we have given intravenous fat emulsion to subtotal gastrectomy patients maintained on well-controlled metabolic regimes similar to regimes of patients who did not receive it. We have maintained isocaloric intakes at 3,000 per day with plenty of K and have noticed no statistical differences in the rate of lean tissue destruction. But that applies only to the first four or five days. After that the patient wants to anabolize, and when you give him a lot of calories he will really climb up the synthetic ladder fast.

DR. CORNELL (Closing).—I would like to thank the discussers for their points. We are the first to admit that this is an extremely small series. We made sure before the study was started that these patients were in good physical shape, except for their operative intervention. These patients had no clinically identifiable cardiovascular disease or any impairment of renal function that we could determine.

Some of these patients received as much as 5 L. of intravenous feeding a day. The investigators do not suggest that this method be applied to the routine postoperative patient. We have utilized the solutions available to accomplish a set of variables, and studies are continuing to enlarge the series.

In connection with Dr. Randall's question, when this study was started we had found initially that Patient B2, despite a large infusion of potassium, nevertheless stayed in negative potassium balance in the immediate postoperative period. This intrigued us somewhat so that we kept increasing the amount of potassium these patients received. In the case of gastrectomized patients, we were not able to revert the potassium balance to any significant positive balance despite, in one patient, an administration of 156 meq. of potassium in a single twenty-four-hour period.

We have studied the CO_2-combining power of these patients in their immediate postoperative period and have been unable to identify any significant change from this large administration of potassium. The solutions we used were everything Dr. Randall said they were. The hypertonic solutions for the caloric source were 25 per cent glucose and 5 per cent alcohol, and we had many technical problems in administering this solution daily.

Patient B4 was a patient who had come into the hospital because of intractable pain from the duodenal ulcer. While in the hospital, he had become partially obstructed and had been treated by an intragastric drip of nitrogen supplied by protein hydrolysate. Prior

to his operation, two days to be exact, the patient's diet had been advanced to a point where he was taking a six-feeding gastric diet two days prior to surgery. This same patient postoperatively received the same amount of nitrogen that Patient B3 did and roughly the same number of calories. This patient weighed 80 kilograms and Patient B3 weighed only 50. We were unable technically to administer, on a weight basis, the same amount of nitrogen to Patient B4 as we were in the case of Patient B3.

In closing, let me say that we do not think that this is a method to be applied to the ordinary postoperative patient. When better solutions are available, this method of feeding may be practical in the patient who is depleted and who requires immediate surgery, or in patients undergoing the radical trauma of radical surgery who manifest a strong and prolonged catabolic response.

THE PRESENT STATUS OF HOMOPLASTY*

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REPORTS in recent years regarding the successful homotransplantation of tissues such as bone and artery have created confusion in the understanding of the entire subject of the grafting of tissue from one individual to another in the same species. It has long been taught that cartilage, cornea, and lens may be homotransplanted successfully, and this success has been attributed to the physiologic common denominator of these three tissues. They lack anatomic vascular trees, their tissues have low metabolic rates, and they survive by nourishment from the intercellular fluids of their new host. In contrast, preserved tissues such as artery and bone are transplanted not as living tissues, but as specific human anatomic structures which eventually are replaced by tissues developed by the repair processes of the host. The latter are referred to erroneously as grafts. In order to clarify this confusion, Longmire has differentiated between the two types of homotransplant and has coined the separate terms "homovital" and "homostatic" grafts.

This presentation reviews the status of the several anatomic tissues and organs and summarizes the present state of our knowledge regarding them. Clinical reports are listed in which homografts of skin have been used successfully as temporary measures. Experimental work which throws light on our understanding of the pathologic processes involved in homotransplantation of skin also is reported herein.

Four excellent reviews[1-4] of the literature upon homologous skin grafts were published in 1950 and 1951. They did much to introduce rational thought and criticism to a subject beleaguered by clinical observations without microscopy, experimentation without controls, case reports without follow-ups, and opinions bereft of logic.

In the decade from 1940 to 1950, Professor P. B. Medawar and his English colleagues provided the basis for current experimentation upon homologous skin transplants. As a working schema, Medawar[5] limited speculation about the causes of failure of skin homotransplants to three hypotheses: blood incompatibility, geneticocellular differences, and acquired active immunity. Until recently the first two of these presumed causes of failure remained hypothetical. It was known that transplants of skin between identical twins were successful permanently but, deservedly, these have been termed autografts. Such grafts have been used to establish parenthood in cases in which there was doubt.[6] With the increasing knowledge of the grouping of blood, several cases have been reported of successful homografts of skin where the donor and recipient had compatible blood groups.[7, 8] However, knowledge of

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systems of blood groupings other than ABO has increased, as has the knowledge of the Rh antigens. Because it is now possible to divide human beings by the ABO, Rh, MNS, P, Kell, Lutheran, Lewis, and Duffy systems with approximately 30,000 blood categories[9] which may be expanded to a million phenotypes, it can be appreciated readily that this approach to the problem is far from exhausted. It has been shown by Medawar[10, 11] that leukocytes (but not red blood cells) and skin share some common antigens. He feels that there are at least seven independent antigens and that 127 skin groups may exist. Longmire[12] has postulated the existence of at least twenty-three skin groups. As yet this must stand as theory because the grouping of individuals by blood and by tissue is more complex than investigators had surmised.

After a lifetime of work, Loeb[13] advanced the theory that tissue incompatibility was due to "organismal differentials." By this term, now more historical than descriptive, Loeb implied complex protein substances, the chemistries of which are individual. This is the theory of inherent or natural immunity. It has been shown that nucleoproteins are antigenic[14] and that proteins which are structurally different are also serologically different.[15] It is also known that ribonucleic acid plays a role in the synthesis of the genes. It is possible that genetic diversity may be associated with antigenic differences. This indicates that the closer the genetic relationship between the donor and the recipient, the greater is the probability that homotransplantation will be successful.[16] The genetic loci which are concerned with the susceptibility and resistance to homotransplants are H-1, H-2, and H-3 (histocompatibility -1, -2, -3).[17] Thus far, however, no differences have been demonstrated in the carbohydrate and protein metabolism between auto- and homografts of skin.[15]

The now popular theory of acquired immunity has received the greatest attention and enthusiasm from investigators. The keystone of this theory is the fact that the second set of homografts of skin from the same donor slough more rapidly than the first.[16, 18] Some investigators attribute this to the Arthus phenomenon in the rabbit.

The rate of loss of homografts of human skin transplanted subsequently in five successive homografts is also accelerated.[19] Dempster[20] has shown that the accelerated rate of loss of the second "crop" of homografts, demonstrated first in the rabbit, can be duplicated in the dog, and therefore does not represent an Arthus phenomenon. Further, he has shown that an initial kidney homotransplant will cause an accelerated rate of loss of subsequent homografts of skin. Also, homografts of skin will cause an accelerated rate of loss of a later homotransplant of the kidney. The time of survival of the secondary homograft is inversely proportional to the size or dosage of the transplant. From this and from experimental evidence, it follows that it is better to use multiple donors in successive transplants to the same individual than several crops from one donor.[21] Medawar expressed the opinion that antibodies generated by homotransplants prevent the completion of cellular mitosis.[22]

Additional evidence which suggests that the loss of homotransplants may be due to acquired immunity is the constant finding of lymphoid cells about the homograft and in increased numbers in the peripheral blood.[23, 24] The mechanism of immunity is understood poorly, and the role of the lymphocyte and of the plasma cell in immunity still is a matter for speculation. However, there is evidence to support the contention that lymphoid cells may be the precursor for or the carrier of immune bodies.[25] The most vulnerable point in the theory of acquired active immunity is the failure of all workers thus far to identify or demonstrate by serologic or by any other means the immune

bodies presumed to be the cause of the failure of homotransplants. It is postulated that the antibodies are at too low a concentration to be detected or that they are removed from the circulation soon after they are formed. The first indirect evidence of the formation of antibodies against skin was shown by the treatment of free donor epidermal cells with the serum of an immunized recipient. The donor epithelial cells were so altered as to be incapable of growth when reimplanted onto the donor.

In experimental animals, some improvement can be achieved in the percentage of successful homografts of skin if the response of immunity is inhibited in the host. Therapy by cortisone and irradiation of the spleen have been utilized to reduce the immune response. Results reported by several investigators have varied. Billingham and associates[26] have prolonged the lives of their homografts of skin by using cortisone locally in the rabbit, while Cannon and Longmire[27] have increased by threefold the number of successful homografts by using cortisone in the chicken. Others have found that cortisone or corticotrophin does not prolong the survival time of homografts of skin in the human being.[28, 29]

Attempts have been made to reduce the ability of the host to respond immunologically by irradiation[30] of the entire body, by splenectomy, by splenic irradiation, and by blocking the reticulo-endothelial system by the use of drugs. It is possible to achieve a high rate of permanently successful homotransplants of skin in the mouse by irradiation of the entire body, and the results are enhanced if the donor also is irradiated.[30] It is difficult to counteract the reticulo-endothelial system in its role in immunity, for regeneration is rapid. Temporary blockage of the reticulo-endothelial function has been effected with trypan blue and with thorium dioxide,[31] but convincing positive results are lacking.

The conjoined placental circulation in synchorial dizygotic freemartin cattle may account for the success of homotransplants of skin between young freemartin cattle. It is presumed that an acquired tolerance exists between the dizygotic twins. An attempt is being made to reproduce this tolerance experimentally in other animals.[32]

Homotransplants have been altered to enhance their acceptance by the host. Freezing has been used to alter the graft.[19] Lyophilization or heating of a homotransplant has been used as an injection into the recipient before the homotransplantation of a second graft of skin. Success of the homotransplants has been increased by this means if the dosage is large, but it has been decreased if the dosage is small.[33-35]

Experiments have been performed in which the recipient has been prepared for the acceptance of a homotransplant by injection of homologous tissue from the same donor, this tissue having been pretreated by lyophilization or by heating.

Homotransplantation of Tissues and Organs Other Than Skin.—

Endocrine tissue: The homotransplantation of parathyroid tissue from stillborn babies to adults after growth upon a culture medium containing plasma from the recipient has been reported. In seven successful transplants reported by Kooreman and Gaillard,[36] the recipient was under 32 years of age. Because these grafts continue their specific physiologic function they are classed as homovital grafts.

Tumor: Tumors are not transplantable when they are in the early, "dependent" stage, but when they grow and become "autonomous," homo- and heterotransplantation are possible (for example, human mammary carcinoma

to the guinea pig).[37] Two types of resistance against tumor transplants are postulated: natural, which prevents the establishment of the tumor initially; and acquired, which causes the tumor to regress after a period of growth. Transplantation of tumors to the anterior ocular chamber is much more successful than to other locations in the mouse. From this, it is felt that natural immunity is by-passed by use of the anterior chamber but that acquired immunity is not overcome.[38-40] Tumor transplants are classed as homovital grafts.

Blood vessels: The homotransplantation of blood vessels has given great impetus to the new field of cardiac surgery. Whereas these grafts appear to represent homostatic transplants which become replaced by the tissues of the host, they serve their function, nevertheless, as patent cylinders with which gaps in vascular continuity can be bridged. In approximately 90 per cent of cases in which homologous aortic grafts have been used in human beings and in experimental animals, the subjects have survived.[41, 42] All layers of the aortic homografts subsequently are replaced by the host. It is felt by Pate that viability of the cells of the vascular homotransplant is not necessary and may be undesirable. Arterial homografts serve as temporary scaffoldings along which a new vessel is fashioned by the recipient. They are, therefore, homostatic grafts. The intima is replaced by a fibrocellular layer from the adjacent ends of the aorta of the recipient. The media is replaced by fibrous tissue. The elastic fibers may persist for at least two years. The adventitia also is replaced by fibrous tissue.[43]

Cartilage: A nonvascularized tissue, cartilage remains relatively unchanged following homotransplantation for approximately two years, then undergoes resorption slowly.[44, 45] The success of cartilaginous homotransplant in the human being, like that of the cornea and lens, is explained by the fact that it does not have a blood vascular system. Cartilage grafts are homostatic.

Kidney: Homologous kidney transplants remain viable for approximately one week in dogs. Their disintegration is accompanied by an infiltration of plasma cells.[46] Human kidney homotransplants have functioned up to five and one-half months,[47] excreting as much as 1,200 to 1,500 c.c. of urine daily. The reason for this variation in time in different species is not determined. Kidney transplants are homovital grafts, but they are successful only temporarily.

Cornea: The cells of corneal homotransplants probably do not survive but are replaced by the host. They seal the anterior chamber and remain transparent initially. Eventually, however, they may become opaque.[48] However, even in their altered, replaced form they may be completely useful. When transplanted to another area, the cornea behaves as any other tissue. It is sloughed and behaves as other tissues when transplanted as a second "crop." Cornea is classed as a homostatic graft.

Bone: It is now generally agreed that homotransplants of bone are replaced eventually by osseous tissue from the host,[49] a process referred to by Phemister[50] as creeping substitution. Bone grafts taken from a bank are classified as homostatic grafts.

Nerve: Transplants of nerves, either autogenous or homologous, were so unsuccessful in large series of cases during World War II as to lead to abandonment of that approach to the problem of bridging large gaps in the continuity of peripheral nerves.[51] Nerve grafts are homostatic since they serve only as anatomic framework along which axons grow from the proximal neural stump in successful transplants.

DEVELOPMENT OF TRANSPARENT CHAMBER TECHNIQUE FOR IN VIVO OBSERVATION OF PHYSIOLOGIC AND PATHOLOGIC CYTOLOGY OF HOMOGRAFTS OF SKIN IN EXPERIMENTAL ANIMALS

Microscopy of cells and tissues in vivo by means of the transparent chamber is a relatively recent development of histologic technique. Pioneer studies of this nature were made by Ziegler[52] in 1875, using diminutive glass chambers. Maximow[53] in 1902, with chambers of celloidin, and of cover glasses, continued the work. He excised the celloidin chambers, after a short period of incarceration in the animal host, for subsequent mounting, sectioning, and staining. In 1924, Sandison[54] evolved the first successful technique for the study of specimens of living tissue over prolonged periods of time. The formidable problem of maintaining quasinormal cell and tissue functions under experimental conditions for periods of days to weeks challenged the ingenuity of other biologists. Clark and Clark,[55, 56] Chalkley,[57] Ebert and coworkers,[58] Algire and Legallais,[59, 60] and many others, attracted by the possibilities of studying physiologic and pharmacologic dynamics of microscopic magnitudes, devoted many years to the perfection of delicate and exacting techniques necessary for the transparent chamber technique of tissue observation in vivo.

Whereas the rabbit, dog, and other mammals of similar size were the usual subjects for experimentation, Algire and his co-workers may be credited with adapting the technique to experimentation with the mouse, which is handled more conveniently in microscopic work. Over a period of ten days or more they have conducted studies involving vascular physiology, neoplastic homotransplantation, and pharmacology. This extensive experimentation has resulted in the refined technique used today. In general, progress in transparent chamber technique has been dependent upon the development of flexible transparent and inert plastics, examples of which are polyethylene, the polystyrene compounds, and Lucite. The Algire chamber has been simplified by Joslin,[61] who has added a banjo-type traction splint (Figs. 1, 2, 3, and 4). The chamber and splint are constructed easily and with few tools from copper wire, solder, and Lucite. The objective in simplifying this experimental technique has been to make it available to clinical investigators whose laboratory time is limited and who lack the facilities of a complete machine shop. Selected strains of mice were used in the experiments from which the following observations were made.

I. *Microscopic Observations (in Vivo) on the Development of Circulation in Autografts of Skin.*—In this study the observations have been made on autografts of skin during the critical fifteen-day period after transplantation, the period during which the success or failure of the graft is determined.

When the chamber is viewed under the microscope immediately following preparation, one is struck by the profuse plasmatic flow. From all sides, floods of extracellular fluid pour into the chamber. If there has been minimal trauma to the panniculus carnosus, there is little escape of blood in the technique of transplantation. A few areas of extravasated blood may be seen but, in general, the chamber and tissues are clear. Multiple arteriovenous shunts are seen. There is oscillation of flow of blood in many vessels. The capillary beds can be seen filling, then emptying as the precapillary sphincter contracts.[62] Vascular engorgement develops rapidly. This varies from stagnation of flow to complete stasis. Incipient thrombosis is seen. The flow of extracellular fluid continues unabated for the first twenty-four hours or so. Cellular elements increase in number and soon it becomes evident that the fluid is becoming increasingly viscous. As time goes on, this viscosity is

so marked that free-flowing lymph with its cellular elements becomes canalized. The "Plasmatische Circulation" of Goldman[63] is observed in action. This is the intermediary source of nutrition of a graft until stromatization

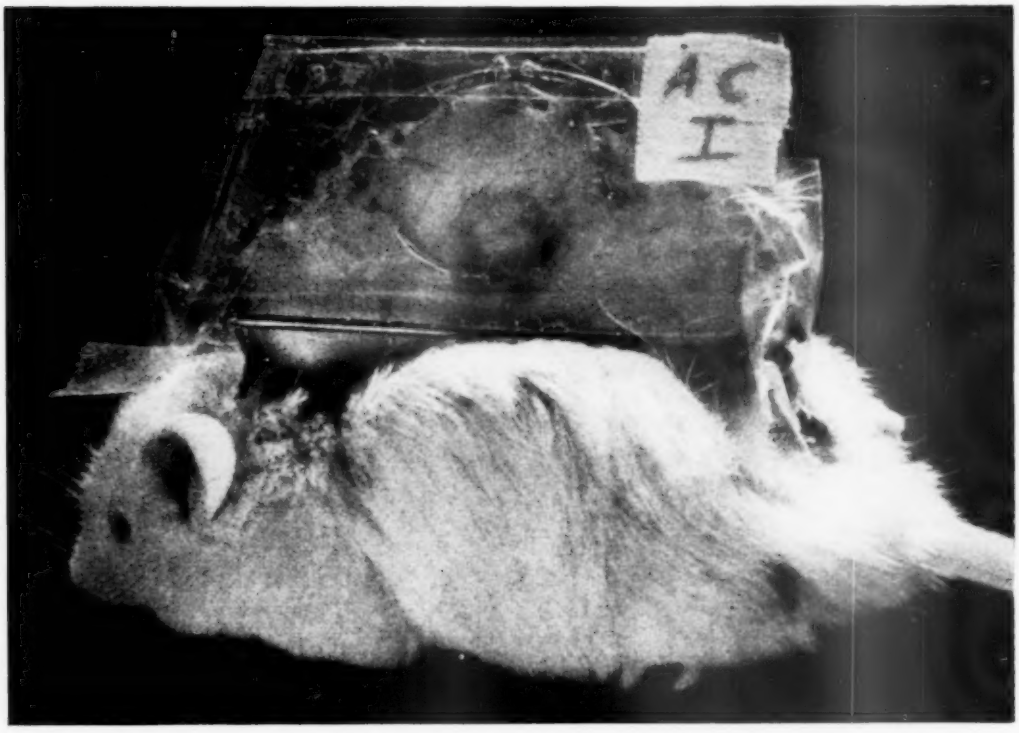


Fig. 1.—Albino Swiss mouse with traction splint and transparent chamber in situ upon the dorsum. A homologous graft of skin can be seen under the chamber, surrounded by a dark halo which represents the recipient bed.

Fig. 2.—Mouse with chamber restrained by cartridge holder. This fits upon mechanical stage of microscope, demonstrated in Fig. 3.

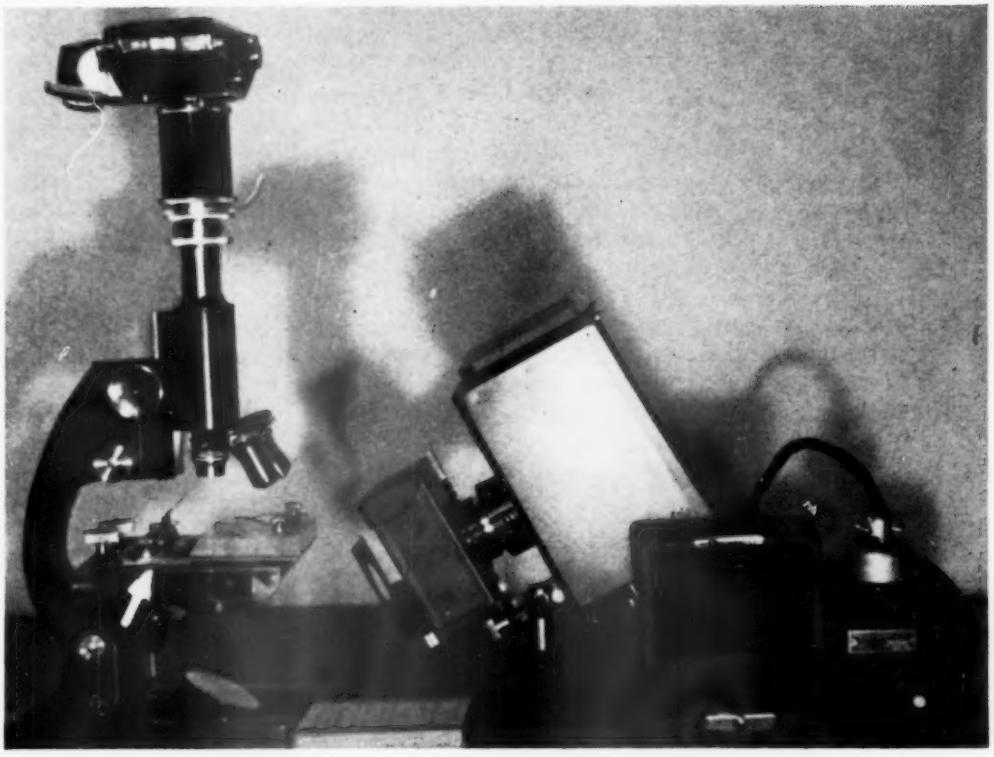


Fig. 3.—Optical system utilized for microscopic observations upon the circulation in auto- and homografts of skin as viewed by means of the transparent tissue chamber. Arrow indicates holder for the cartridge which is placed upon the mechanical stage. (From *Plastic and Reconstructive Surgery.*)

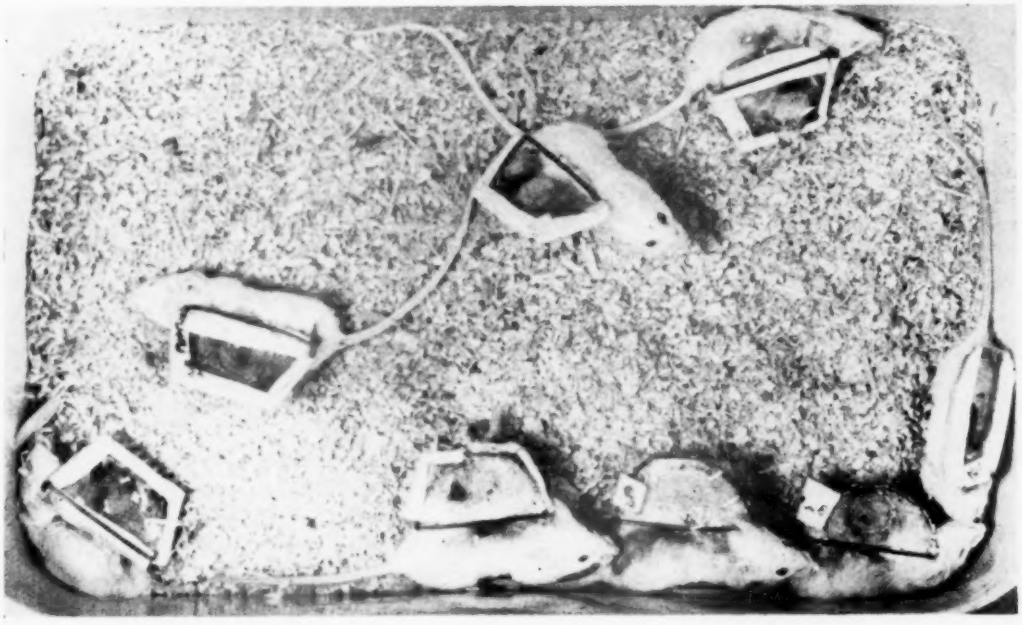


Fig. 4.—Colony of eight mice with transparent tissue chambers in situ upon the dorsum of each animal.

occurs. It is clear that necrosis of the graft will follow if its cellular components do not receive nourishment and if the products of metabolism of the cells are not removed in the ten-day period before the young capillary buds assume these functions. During this interim the circulation of extravascular fluid is the sole means of supply of nutritional elements. Despite this, some autolysis of cells may be observed in the unstained specimen.

There arises the question as to whether there is ingrowth of vessels from surrounding or from underlying tissues, subadjacent to the graft. In our observations the growth was predominant from the peripheral tissues, not from the underlying tissues. As the process develops, one is impressed with the seemingly purposeful orientation of the capillary sprouts as they grow, always toward the graft, turning sharply toward it soon after budding from the mother vessel, so that their arborization consists of many nearly parallel branches. The question presents as to whether this parallelism of the young vessels is the response to a chemotactic stimulus (Fig. 5).

Fig. 5.—The pattern of neovascularization of an autograft of skin 14 days old, which shows the characteristic distribution of new vessels which are coursing parallel to one another and vascularizing the autograft from its perimeter. This is a permanent type of hemic circulation. *G* indicates the graft. (From *Plastic and Reconstructive Surgery.*)

The use of the transparent chamber technique has afforded the observation that the grafts which have been successful have been those in which the blood vessels of the recipient area have remained patent and have exhibited active circulation. Once a vessel becomes thrombosed, it jeopardizes the "take" of the graft, for it has not been observed that the vessel can recanalize sufficiently in time to play a helpful role in the "take" of the graft. Grossly, the grafts are pinkish white at first. Little activity can be observed in the recipient bed other than the normal flow of circulation in the patent vessels farther

away. However, after four to six days, small ball-like projections can be seen upon tiny offshoots of vessels. These are capillary buds of ingrowing vessels. Blood will flow in these vessels eight to nine days after transplantation of the autograft. At this time one can see the circulation, which moves alternately in opposite directions. This phenomenon lasts for only a few days, following which time the hemodynamics of the situation apparently dictate the direction of flow in the capillaries under observation. This budding process of ingrowing vessels reaches its maximum from the seventh to the tenth day after transplantation and, because of an unknown factor (called chemotaxis for want of a better name), these vessels grow toward the graft. There is no increase in vascular growth in any direction other than toward the skin graft, and from the tenth to the twelfth day these vessels line up in nearly parallel fashion, all growing toward the skin graft. After the twelfth day they are present in such profuse numbers that a definite areola of vessels surrounds the graft. This can be seen microscopically and macroscopically. The graft becomes more opaque, macroscopically, from the seventh day on and, although there is no certainty as to the vascularization which takes place from the bed to the underside of the graft, at this time the graft becomes more opaque. Dark spots are observed in the area of the graft itself. These have been interpreted as on-end views of new vessels. Small vessels are seen to grow into the graft from the floor of the recipient bed on the ninth day.

The development of a mosaic type of pattern, which appears in the recipient bed as early as the first day after transplantation, appears to be due to desiccation of the adipose tissue of the subadjacent bed of the host. Later, globules appear in the field which look like fat droplets which have coalesced. These have been observed the ninth day after transplantation.[64, 65]

II. *Microscopic Observations (in Vivo) on the Development of Circulation in Homografts of Skin.*—

A. *Control homografts:* This report is intended to record morphologic and physiologic observations on the development of early circulation in homografts of skin in animals.

Thirty-eight mice were subjected to homotransplants of skin. To exclude the possibility of success because of syngenesiotransplantation, transplants were made between mice of widely diverse strains. *The development of multiple minute thromboses of the vascular circulation of the recipient bed is the outstanding morphologic change* (Fig. 6). Thrombosis occurred any time from one to ten days after homotransplantation. This was observed to be followed by the development of coagulative necrosis and slough of the infarcted area which included the graft (Fig. 7). The phenomenon of invasion of the graft by young capillaries and the establishment of an active and sustaining neovascular hemic circulation (as observed in autografts) was not observed in a single preparation in the homograft series. Observations by the tissue chamber technique on the circulatory pattern of homografts of skin were characterized by excessive turbidity of the extracellular plasmatic circulation, by degeneration of extracellular fat during the first three days after transplantation, by the development of multiple thromboses in the vessels of the recipient bed one to ten days after transplantation, by the failure of any capillaries to invade the homoplastic graft, and, finally, by the thinning of the graft antecedent to its complete necrosis. Homografts of skin transplanted to mice showed an average period of viability of 5.6 days.[66]

B. *Homografts to treated recipients:*

1. *Homografts to mice treated with corticotrophin:* Homologous skin grafts were transplanted onto the dorsal regions of eight adult mice that were treated with ACTH. Corticotrophin (ACTH) was administered with the

knowledge that it mitigates the allergic response and may reduce the level of circulating antibodies,[67, 69] for the most popular theory of today is that homologous skin transplants fail because of acquired immunity or sensitivity. The equivalent of therapeutic doses of ACTH for the human being was administered daily, and the responses of the recipients were assayed by the degree of depression of circulating eosinophils and by clinical and microscopic observation of the grafts in situ. Solution of corticotrophin, diluted with saline solution and preserved by refrigeration, was given intramuscularly in daily doses of 0.14 mg. Some of the animals developed hyperactivity which bordered on mania. This was exemplified by hyperreflexia, viciousness, and overexertion. Eight adult mice were so treated, and homologous grafts of skin were then transplanted to them. In three of these, the development of

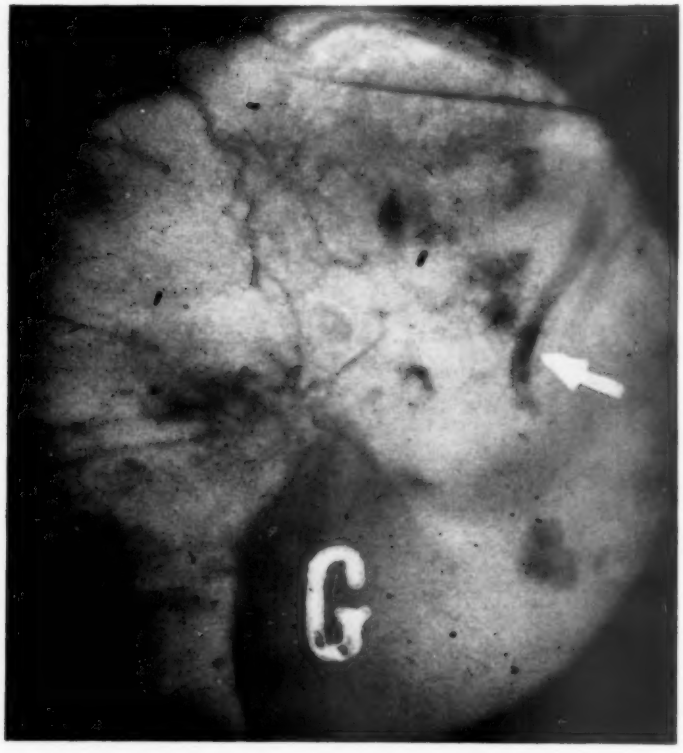


Fig. 6.—Beginning thrombosis of vessels of recipient bed following the transplantation of a homograft of skin. No neovascularization can be seen and the sharp outline of a thrombus can be visualized (indicated by arrow) in one of the main cutaneous vessels of the recipient bed. *G* indicates the graft.

diffuse thromboses in the small vessels of the recipient bed was observed as in control animals. In the other five animals, thromboses did not develop. Capillary budding and neovascular growth were virtually nonexistent. No vessels were in proximity to the graft when nourishment by plasmatic circulation ceased. It is postulated that corticotrophin suppressed mitosis of the angioblasts. Vascular stromatization to preserve the viability of the grafts therefore was impossible. The homoplastic grafts failed to survive in all animals treated with corticotrophin. Apparently corticotrophin limited the development of thromboses and prolonged the life of homografts of skin, but did not prevent their later necrosis. Homografts to mice treated with corticotrophin showed an average period of viability of twelve days.[70]

2. *Homografts to mice treated with Dicumarol:* The consistent thrombosis of the blood vessels in the recipient bed of mice to which homoplastic grafts of skin had been transplanted led to the use of an anticoagulant in a series of seven mice. It was felt that if thrombosis could be prevented, homotransplants of skin could be sustained by means of the plasmatic circulation for a longer period of time, for the plasmatic circulation endures only as long as does the regional hemic circulation. Dicumarol was used because of its easy administration by mouth. The feeding schedule of Overman[71] was used. The recipient mice were fed 2 mg. of Dicumarol daily. It was found that, after four days, their prothrombin times were doubled. A maintenance dose of 2 mg. every third day was found to sustain the level of prolonged prothrombin time. After two to four days of Dicumarol therapy, homoplastic

Fig. 7.—Complete absence of new vessels about the perimeter of a 10-day-old homograft of skin. The recipient bed developed multiple thromboses from one to ten days following transplantation, and no capillaries have been observed entering the graft to nourish it permanently. Without either a hemic or plasmatic circulation, these grafts failed within six days upon an average. *G* indicates the graft. (From *Plastic and Reconstructive Surgery.*)

grafts of skin were transplanted to the dorsal thoracic regions of the treated animals. The hemic circulation of the tissues of the recipient bed remained active for as long as twelve days in the seven mice which had been treated previously with Dicumarol. During the initial twelve days following the transplantation of homologous skin grafts, the plasmatic and hemic circulations were as active or more active than those in untreated animals following autogenous transplantation of skin. A greater number of capillaries and venules functioned actively, and the rate of circulation was more rapid. Capillary buds appeared abundantly, and neovascularization proceeded apace with new vessels growing toward the graft. Between the twelfth and twenty-first days the hemic circulation slowed and finally stopped. Following multiple thromboses, the homologous skin transplants sloughed. However, in

the animals in which thrombosis did not develop, the new vessels grew up to the homologous skin graft, and then turned and coursed around the graft. New vessels arranged themselves around the periphery of the graft in concentric circles, giving the appearance of vascular lamellae (Fig. 8). No penetration of the new vessels into the graft was observed. Nourishment, by the hemic circulation, did not develop. The plasmatic circulation ran its course eventually, and the homologous skin grafts failed because of the lack of stromatization. None of these homotransplants persisted beyond the twenty-first day. Homografts to mice treated with Dicumarol showed an average period of viability of fourteen days.[72]

Fig. 8.—Active new vessels coursing about the perimeter of a homologous skin graft which is 14 days old. The conditions in the recipient were altered by administering Dicumarol to prevent development of multiple thromboses, which has been observed to be the primary cause of failure of homografts of skin. The new vessels, which formed in abundance, did not grow into the graft, however, to nourish it permanently, but coursed about the perimeter, forming a pattern of peripheral concentric lamellae. An inimicable state appeared to exist between the new vessels which had formed and the homologous skin transplant, preventing its stromatization. With the continued hemic and plasmatic circulation in the bed, these transplants endured for approximately twelve days. *G* indicates the graft.

3. *Homografts to mice treated with Dicumarol and potassium hyaluronate:* Experimental observations were made upon the activity of the vascular bed in thirteen recipient animals treated with Dicumarol in which homologous grafts of skin were made adherent through the use of potassium hyaluronate. Wyburn and Bacsich[73] observed that tissues which can be transplanted homologously in man—hyaline cartilage, cornea, and lens—all are avascular, but they also pointed out that these tissues consist almost wholly of mucoprotein, of which hyaluronic acid is one polysaccharide. These

authors felt that all mucoproteins are nonantigenic and might confer this nonantigenic property to adjacent tissues.

With the intent of conferring this nonantigenic property to homologous skin grafts, potassium hyaluronate was used in a series of thirteen mice. All these animals were pretreated with an anticoagulant (Dicumarol) to prevent failure of the grafts due to thrombosis. The vascular bed remained patent, and the rate of circulation was rapid. In these animals there was increasing diapedesis, extravasation, and hemolysis of red blood cells. The translucency of the field disappeared as the ground-glass appearance, typical of impending failure of the transplant, became evident. Stigmas associated with successful autografts of skin—capillary budding, parallelism of vessels, and areola formation—were lacking in this group of experimental animals. None of these homologous skin grafts was successful. From this we concluded either that potassium hyaluronate was ineffective in nullifying the hypothetical immune response of the host to homologous skin grafts or that immunity is unassociated with the failure of ingrowth of new vessels into homologous transplants of skin. Skin homografts to mice treated with Dicumarol and potassium hyaluronate showed an average period of viability of twelve days.[74]

4. *Homografts to mice treated with intraperitoneal injections of homologous skin filtrate:* Observations were made upon homografts in sixteen mice that had been pretreated with intraperitoneal injections of homologous skin filtrate. A weighed quantity of depilated mouse skin was ground with sand and extracted with normal saline solution. The extract was passed through a Seitz filter. The weight of skins being known, and the filtrate being made up to convenient volume, the strength of the extract could then be expressed in terms of milligrams per cubic centimeter of skin equivalent. Mice were given intraperitoneal doses of varying strength at two-day intervals in an attempt to determine potency. No untoward effects due to the extract were observed. None of the homografts of skin was successful in this group of animals. In the mice treated with homologous skin filtrate, the rate of autolysis of the graft was *accelerated strikingly* over that in control animals. The intraperitoneal injection of homologous skin filtrate caused an accelerated loss of the homograft of skin which was transplanted subsequently, acting much the same as the second of two sets of homografts transplanted successively. These observations are in keeping with those of the Arthus reaction observed by Medawar. In mice treated with homologous skin filtrate, there was active engorgement of the vessels of the panniculus of the opposite and ungrafted side fo the skin fold, suggesting a generalized vascular reaction to the filtrate. It was presumed that the filtrate contained a factor, the nature of which is unknown, which was responsible for the more rapid necrosis of homografts and for the variation in the vascular pattern in animals treated with it when compared with behavior of homografts of skin in untreated animals. Homografts to mice treated with intraperitoneal injections of homologous skin filtrate showed an average period of viability of only three days.[74]

5. *Homografts to mice treated with Benadryl:* In this study, twenty-two mice were treated with an antihistaminic to test the assumption that allergy, immunity, or sensitivity may cause failure of homologous grafts of skin. Antihistaminics have advantages in this study over corticotrophin (ACTH), for the possibilities that thrombosis occurs on the basis of hypercoagulability or the failure of capillaries to invade the graft due to retarded mitosis and cellular growth are eliminated when antihistaminics are used. Mice were given oral feedings of Benadryl in doses equivalent to therapeutic doses in the human being for one week prior to homotransplantation. A daily maintenance dose of 29 gammas was given to each animal during the period of observation.

Of the twenty-two mice studied, nine exhibited grafts which ran the course characteristic of untreated homografts and failed within ten days. The cause of their failure was thrombosis of the vessels in the recipient bed followed by necrosis of the graft. Thirteen grafts exceeded the maximum survival period (ten days) of untreated homografts. Of the grafts that survived beyond ten days, the circulation in the recipient bed continued to be active. In no instance did these grafts show evidence of invasion by capillaries. In one animal, parallel vessels were directed toward the graft on the tenth day after transplantation, but multiple thromboses of the vessels began on the fourteenth day and this development was followed by the failure of the graft. In this animal, necrosis of the graft resulted from failure of new vessels to invade

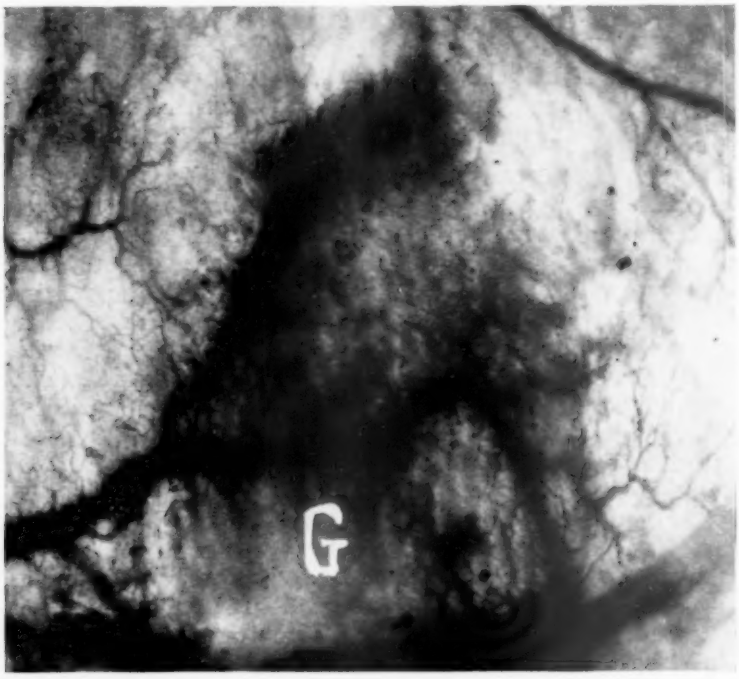


Fig. 9.—Homograft of skin upon recipient animal which was treated with an antihistaminic (Histadyl). Vascularization from the recipient bed is evidenced along the course of one of the main underlying vascular channels of the bed. This type and amount of vascularization were seen from seven to nine days following homotransplantation in animals treated with Histadyl or with sodium salicylate. It was also seen when the recipient bed was treated with heavy irradiation prior to homotransplantation. This is a transient type of circulation which disappears shortly after it is first observed. In none of these transplants was a permanent hemic circulation established with certainty. However, because of the transient type of circulation from the recipient bed, these transplants endure for as long as fourteen days. This is true of transplants vascularized in similar fashion in recipients which have been previously irradiated. *G* indicates the graft.

the graft and to nourish it permanently. In most of the animals the circulation in the recipient bed continued to be active. However, the rate of flow in vessels adjacent to the graft was greatly reduced as compared to that in more peripheral vessels of the recipient bed. New capillaries were seen to appear, but these vessels were not arranged in an orderly, purposeful manner to facilitate their invasion of the graft. These grafts remained viable until the time when the graft could no longer survive on a plasmatic circulation. Their failure was due to the inability of the host to establish a permanent hemic circulation for the graft. Homografts to mice treated with Benadryl showed an average period of viability of twelve days.[75]

6. *Homografts to mice treated with Histadyl:* In this study forty mice were treated with a drug which supplies approximately sixteen times more antihistamine than Benadryl. Histadyl was dissolved in sterile saline solution and injected intraperitoneally immediately following homotransplantation and each day thereafter during the period of observation. In contradistinction to experiments in which Benadryl was used, revascularization of the graft by capillaries was seen as early as seven days. In each instance, capillary invasion of the graft occurred from the recipient bed immediately subjacent to the transplant (Fig. 9). The pattern of revascularization was correlated with the pattern of underlying vessels in the bed of the host. That portion of the transplant that overlaid large vessels in the recipient bed became vascularized first. The new capillaries were soon engorged with blood. Subsequent stasis and thrombosis, however, preceded endothelial rupture, which occurred invariably. The grafts were rendered asvascular. Vascularization from the peripheral portion of the recipient bed was not observed, and a permanent hemic circulation was not established in any of the homografts. The longest survival was thirty-four days, and the average survival of homotransplants in recipients treated with Histadyl was 16.4 days.

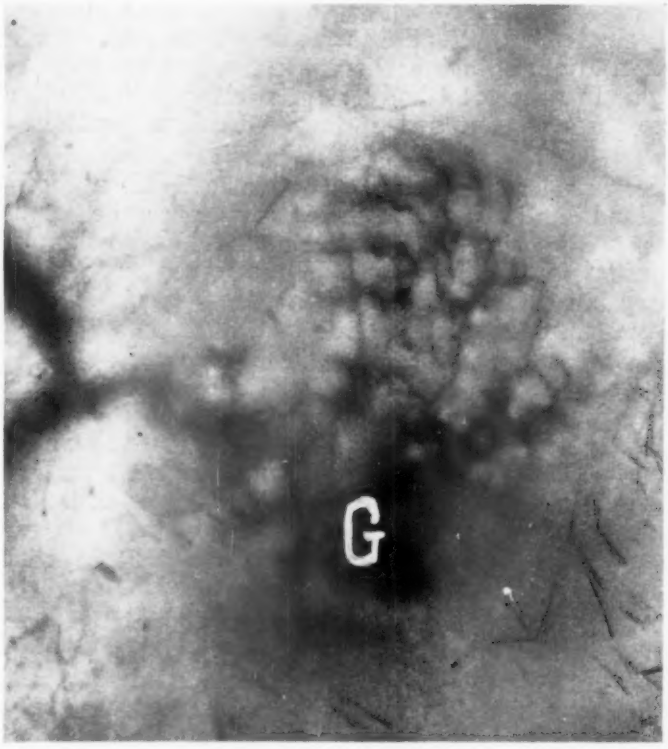


Fig. 10.—Homograft of skin upon a recipient animal which was treated with sodium salicylate. A transient circulation has developed from the recipient bed. This appeared at seven days and disappeared at nine days.

7. *Homografts to mice treated with sodium salicylate:* In this study forty mice were treated with intraperitoneal injections of 4.5 mg. of sodium salicylate upon the day of homotransplantation and for each day thereafter during the period of observation. An increasingly viscid exudate characterized the early plasmatic circulation. Capillary vascularization of the graft was evident within seven days. This occurred from vessels of the host lying

beneath the transplanted tissue (Fig. 10). The vascularization of the graft was transient, and the capillaries failed to differentiate into arterioles and venules. Rupture of the vessels caused extravasation and hemolysis of the blood. Peripheral vessels of the recipient bed did not invade the graft. The average survival time of homografts thus treated was 12.1 days.

8. *Homografts to mice in whom the recipient area was irradiated prior to homotransplantation:* In this study twenty mice were irradiated twice weekly for a period of two weeks. They received 400 r at the time of each treatment. A total of 1,600 r was administered to the local recipient site upon the dorsum of the mouse. These animals were treated with x-ray because it is thought to lower the ability of the organism to develop antigens.

Benjamin and Sluka[76] found that animals irradiated before the injection of beef serum had a lower precipitin titer, and this antigen disappeared more slowly than in control animals. Hektoen[77] found that the production of lysin for red blood cells was reduced in irradiated animals. Numerous workers have shown that irradiation lowers the resistance of animals to transplanted tumors. Previous investigators have attempted to suppress antibody formation by a single dose of total body irradiation. Rabinovici[78] utilized a dosage of 500 r in 1947. Dempster, Lennox, and Boag,[79] in 1950, utilized a dosage of 250 r twenty-four hours prior to homotransplantation. Hardin and Werder[80] administered a single dose of 300 r to the whole body twenty-four hours prior to homotransplantation. Since earlier investigators have used low dosages of irradiation applied to the total body, it was felt that irradiation should be applied locally to the recipient bed of the future homograft in relatively high doses.

Twenty mice were irradiated, and an active hemic circulation of the recipient bed was maintained in all of the animals. Striking was the definite and tortuous vascular plexus at the perimeter of the recipient bed following homotransplantation. This capillary plexus was visible macroscopically by the ninth day. Definite capillary invasion of the grafts from the subadjacent tissue was noticed within nine days. A definite flow of formed elements of blood was observed. On approximately the twenty-first day, when the splints and chambers had loosened, these were removed in a few of the animals and the transplants were observed macroscopically thereafter. It was not difficult to follow the progress of pigmented grafts upon nonpigmented recipients and vice versa. These grafts apparently have maintained themselves as far as macroscopic evidence is concerned, although they have failed to grow hair. This is a sequel to the previous treatment by x-ray, apparently. The longest survival was a homograft followed for twenty-four days in the chamber and for forty-eight days with macroscopic observations. The average survival was 15.1 days.

C. *Homografts treated by subcutaneous autoburial prior to homologous transplantation:* Because of its numerous and specialized functions, skin must be considered an organ. Embryologically, skin is derived from ectoderm and mesoderm. Its ectodermal derivatives consist of epidermis and the adnexal structures; namely, the pilosebaceous apparatus, sweat glands, and, in specialized regions, the apocrine glands. The mesodermal portion, the dermis, is differentiated into papillary and reticular layers at approximately the third month of embryonic life, and elastic fibers appear during the fifth month. The problem of homotransplantation of skin may pivot upon this dual embryologic derivation.

The burial of skin has been utilized by many surgeons in the repair of hernia (Loewy,[81] 1913; Rehn,[82] 1914; Eitner,[83] 1920; Peer and Paddock,[84] 1937; Uihlein,[85] 1939; Mair,[86] 1945). After burial for approximately two years, the ectodermal elements are destroyed beyond histologic recognition. It is known that homotransplants of dermis taken by the usual surgical means are not free

of adnexal structures even though the epidermis has been removed by razor dissection. An endeavor to split skin into its component parts of epidermis and dermis was made by Billingham and Reynolds,[87] who loosened the epidermis by using trypsin. They transplanted autogenous sheets of cells from the epidermis. The experiments reported herein were undertaken with the thought that through subcutaneous autoburial, skin might be rendered devoid of its adnexal structures. In short, an attempt was made in this experiment to produce atrophy of the cutaneous appendages by burying skin in a mouse, recovering this skin at a later date, transplanting it to a second mouse of high genetic diversity, and observing the development of circulation by the transparent chamber technique.

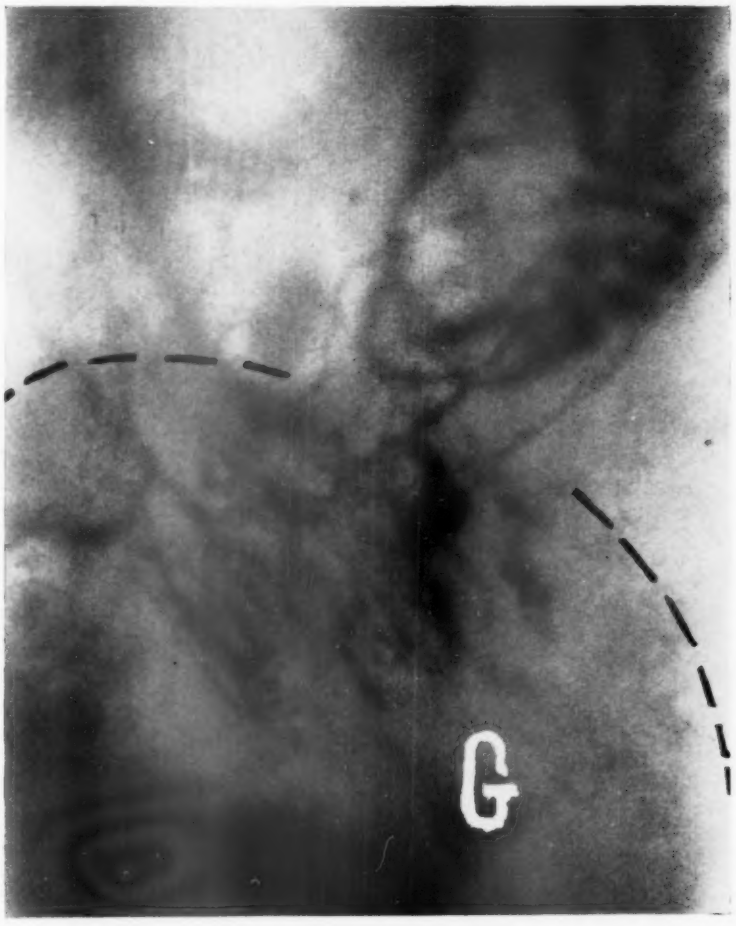
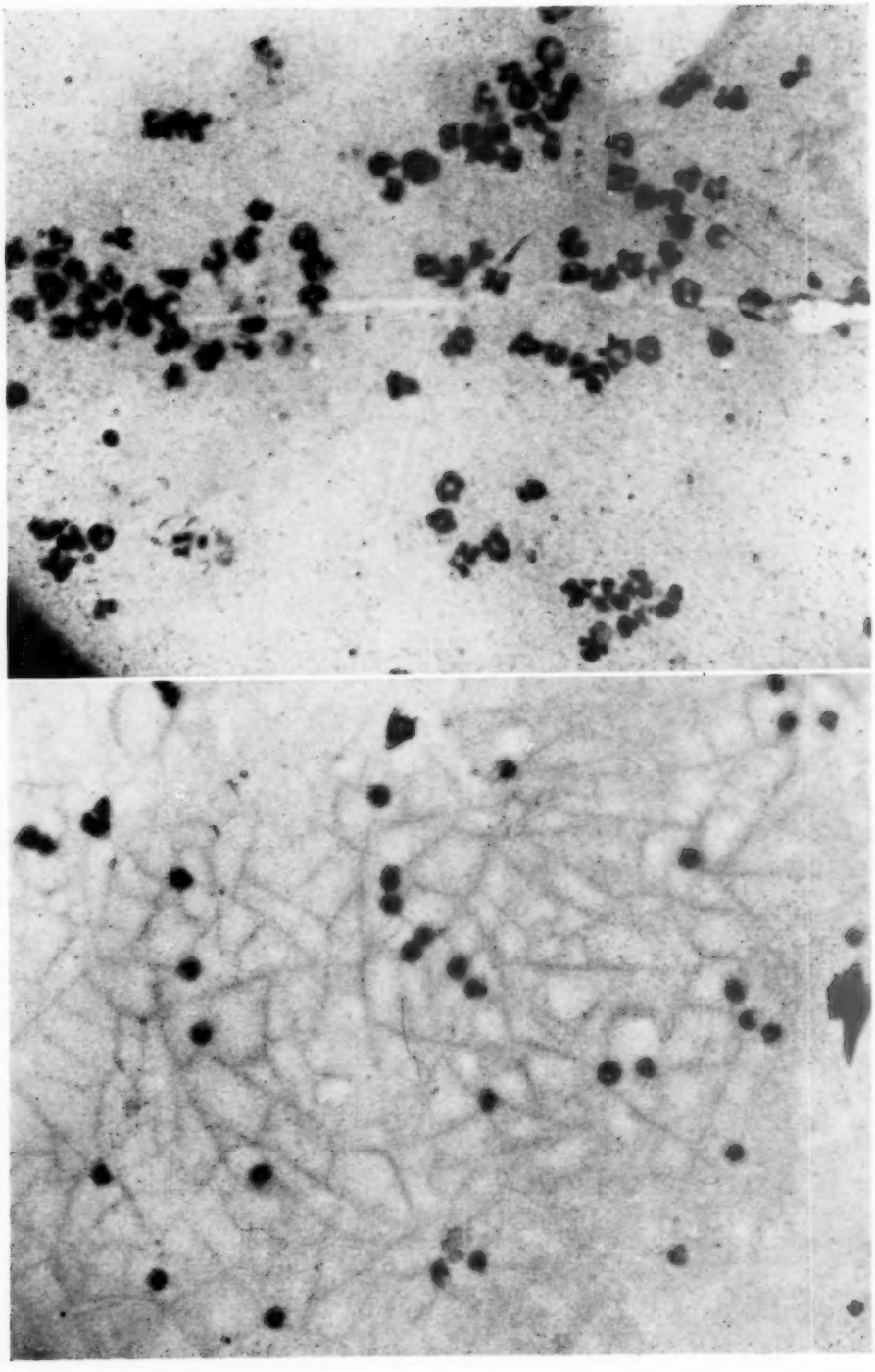


Fig. 11.—Homologous graft of skin altered by burial prior to homotransplantation, showing an abortive type of vascularization about the periphery of the homotransplant. New vessels proceeded toward the graft, but stopped at its periphery and turned back to the recipient bed, forming multiple vascular loops. The blood coursed rapidly about the loops or shunts and did not appear to take the function of nourishing the graft. These grafts, however, endured approximately fourteen days. *G* indicates the graft.

The burying of grafts was accomplished by excising a free graft of whole-thickness skin (approximately 1 cm. square) from the dorsum of a mouse. The surrounding skin was undermined, the free graft was replaced on its bed, and the two marginal flaps of skin and subcutaneous tissue were sutured over it so that the original graft was completely covered. These buried autogenous grafts were recovered at various intervals and transplanted homologously. The opti-

A.



B.

Fig. 12.—Smears made of the plasmatic transudate and exudate which surrounded (*A*) an autograft and (*B*) a homograft. The fluid around autografts of skin showed that leukocytes were present four days following transplantation, 90 per cent of which were polymorphonuclear. Fluid around homografts of skin yielded 20 to 50 per cent lymphocytes present as early as two days following transplantation. It is possible that these lymphocytes are the carriers of or precursors of immune bodies.

mum burial time for homografts is between seven and seventeen days, inasmuch as grafts so prepared survived for the greatest number of days, an average of eighteen days. Capillary invasion at the periphery of the graft was noted (Fig. 11). These capillaries form shunts or loops. This abortive form of circulation was insufficient to nourish the transplants permanently. Skin buried in mice in excess of four weeks is extremely difficult to recover, for it is altered to such a degree that it cannot be identified. Microscopic examination of skin buried for short periods of time shows diminution in the amount of keratin and involution of approximately one-half of the sebaceous glands. Hair follicles appear unchanged. Occasionally, leukocytic infiltration into the dermis is noted. In this experiment, twenty-four buried grafts were observed under the microscope. The average viability time of these grafts was fourteen days. One graft was observed for thirty-eight days, at which time the animal was sacrificed although circulation persisted in the recipient bed.[88]

D. *Study of cellular exudate surrounding a homograft of skin:* Utilizing a micropipette, plasmatic transudate and exudate were obtained through perforations in the tissue chamber from the area around the graft. Smears were made of this material and visualized by the use of Wright's stain. Fluid around autografts of skin showed that leukocytes are present four days following transplantation, 90 per cent of which were polymorphonuclear (Fig. 12). Fluid around homografts of skin yielded 20 to 50 per cent of lymphocytes which were present as early as two days following transplantation.

DISCUSSION OF LABORATORY DATA

From these experiments, carried out over four years' time, it appears that the mechanism of failure of homografts of skin is complex, consisting of several phases.

The skin appears to evoke a response which simulates immunity, causing an early failure of the transplants due to thrombosis of the vessels of the recipient bed. This response is presumed to be one of immunity because it can be blocked partially by corticotrophin, Benadryl, Histadyl, and salicylates. Evidence that it may be initiated by the epidermis is at hand, for the response is not as prompt or complete if homologous transplants of dermis, virtually free of cutaneous adnexa, are used.

Lymphoid cells (lymphocytes and plasma cells) appear early in the plasmatic circulation around homografts. These may be the carriers of or the precursors of immune bodies or toxins which initiate thromboses of the vessels in the recipient bed of the host. Once the hemic circulation ceases, the dependent circulation slows to a halt, and the homotransplant of skin undergoes necrosis.

When the phenomenon of clotting is blocked by the use of Dicumarol, new capillaries grow up to and encircle the homograft, but they do not invade it to nourish it permanently, for an inimicable state appears to exist between the newly formed capillaries and the homograft. This state can be limited if Histadyl or salicylates are administered to the recipient or if the recipient site is irradiated. However, in spite of incipient vascularization of the homograft from the bed of the host, the new capillaries soon undergo rhexis and dissolution. The permanent vascularization of homotransplants of skin has not been observed in any of these experiments.

CLINICAL OBSERVATIONS ON HOMOGRAFTS OF SKIN

Laboratory data as reported previously were utilized in practical observation of homografts of skin in the human being. The phenomenon, as observed in animals, of the development of thromboses of the recipient bed to which homoplastic grafts were transplanted was utilized practically in the control of hemorrhage from a large open wound in a hemophiliac person. The case reports follow.

Fig. 13.—Incised wound of the forearm for release of an expanding hematoma following trauma in a patient with hemophilia. The incision was carried through the antebrachial fascia down to the interosseous ligament as an emergency procedure because of absence of radial and ulnar pulses with impending gangrene (Case 1).

Fig. 14.—The wound following attempts to control hemorrhage. Pieces of Gelfoam are adherent to the wound (Case 1).

CASE 1.—C. J., New York Hospital case No. 239923, *exsanguinating hemorrhage from a large wound in a hemophiliac person controlled by homoplastic graft of skin.* A 23-year-old mail clerk had been known to be hemophiliac since the age of 9 months. He had been hospitalized seventeen times previously at the New York Hospital and at least three times in other institutions for episodes of uncontrolled hemorrhage. Upon two occasions the patient suffered from bleeding associated with fractures of the right and left tibia and left femur. There had been numerous episodes of hemarthroses of both knees, the elbows, and of the joints of the hands, complicated by pressure paralysis of the extensors of the left wrist. Upon several occasions he suffered from subarachnoid hemorrhages, hematuria, and bleeding following the extraction of teeth.

On the day prior to his sixteenth admission to the New York Hospital, the patient caught the right forearm in the door of a car. He suffered pain, and the arm became so

swollen that extension of the elbow beyond eighty degrees was impossible. It was evident from the progressive blanching of the digits, increasing nerve palsies, and weakening of the radial pulse that the patient had sustained an expanding hematoma. Because of ischemia of the fingers, digital anesthesis, and impending gangrene, the forearm was

Fig. 15.—Homologous skin graft taken from patient's father utilized to promote thrombosis of the bleeding wound in this patient who was known to be hemophiliac. Multiple perforations were made in the graft to prevent the lifting of the graft from the wound by accumulations of blood. The tails of the marginal sutures were tied securely to each other over a bulky bolus of cotton waste. The extremity was immobilized by a light plaster splint (Case 1).

Fig. 16.—Thirty days after it had "taken" successfully and caused a cessation of hemorrhage, the homologous skin graft melted away. Photograph of wound after homologous skin graft had been removed and the wound had been cleansed with frequent changes of wet dressings. It was still bleeding actively and there was a paucity of granulation tissue (Case 1).

incised and the antebrachial fascia was opened down to the lacertus fibrosus and the transverse carpal ligament (Fig. 13). This operation was performed by another surgeon. Discussion of the validity of this bold management of the problem is not within the scope of this paper. The circulation returned to the hand, but the wound oozed blood for four

days, during which the patient was given multiple transfusions of fresh blood and anti-hemophilic plasma (Fig. 14). Upon the fourth day it was necessary to give 1,500 c.c. of blood in a period of twelve hours. In spite of persistent ooze of blood from the wound, a skin graft was ltaken from the patient's father and transplanted to the wound of the forearm (Fig. 15). A homoplastic skin graft was used as an emergency measure because an autogenous graft certainly would leave a bleeding donor site. An equally important reason for the use of a homoplastic graft was the knowledge that such grafts of skin cause thrombosis of the vessels of the bed of the recipient.

Fig. 17.—The donor sites of the anterior and medial thigh healed uneventfully under the influence of the hourly transfusions of freshly drawn whole blood which were administered during the twenty-four-hour period after cutting and transferring the skin graft (Case 1).

Fig. 18.—Appearance of the wound covered with a surfacing autograft of thick-split skin. This has held up well and has proved a durable surface.

The homograft of skin was successful; the bleeding from the arm ceased. The homograft soon showed signs of dissolution, characterized by a shiny appearance of the graft as it began to thin. Small marginal wounds developed and started to bleed (Fig.

16). Forty days following homotransplantation, the homoplastic graft was excised and an autograft (from the patient's thigh) was transplanted to the wound of the forearm. Forty-eight hours later it was necessary to evacuate a hematoma from beneath the graft. Pressure was reapplied. The graft was completely successful and physiotherapy was instituted to aid in restoration of impaired function of the hand and arm (Figs. 17 and 18).

Fig. 19.—*A*, Appearance of wound of leg in a 31-year-old Negress one year after the onset of a phagedenic ulceration of the leg (due to micro-aerophilic organisms) which spread to the donor site (*B*) of the thigh, following the cutting of a skin graft from that area (Case 3).

The daring necessary for the cutting of an autogenous skin graft was supported by the management* of the hematologic crisis. One hundred to one hundred fifty cubic centimeters of fresh blood (uncitrated) was given every twenty-four hours on the theory that the transfused blood would supply sufficient normal clotting mechanism to achieve primary healing of the donor site and adherence of the graft. Search of the literature reveals no reported instances in which the role of homografts of skin in the purposeful production of multiple thromboses in recipient bleeding wounds has been used clinically.

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The management of necessary surgery during a bleeding crisis by the frequent administration of repeated small transfusions of fresh uncitrated blood is a lifesaving measure which has not been emphasized in the surgical literature.[89]

CASE 2.—H. P., New York Hospital case No. 545256, *third degree burn causing loss of skin of 50 per cent of surface area of the body treated by temporary use of homologous skin; subsequent replacement by autogenous skin grafts; development of Curling's ulcer by the donor.* A 5-year-old white boy was admitted to the hospital three weeks following third degree gasoline burns of the right forearm, buttock, perineum, genitals, and both lower extremities, involving 50 per cent of the body surface. This boy had been treated by his local doctor with 20 units of plasma and a total of 5,250 c.c. of blood. In addition, he received chemotherapy and Cortate. The burns had been treated locally by petrolatum gauze and pressure dressings.

Fig. 20.—Clean bed of granulations upon leg and thigh prior to the use of homologous grafts of skin (Case 3).

The patient was given a saline bath three times daily. He tolerated this treatment well. Because of the boy's inanition and the paucity of donor sites, skin was taken from his father. Patterns of the unhealed wounds demonstrated a surface defect of nearly 500 square inches. Eighteen dermatome drums of skin were cut from the parent's torso and lower extremities.

The transplantation of the homografts was successful, and the patient progressed favorably for the following six weeks, when the homotransplants thinned and began to undergo dissolution. The remaining homografted skin was excised and autografts were taken from the back and transplanted to the legs. These grafts failed. Because he began to develop foot drop bilaterally, the patient's lower extremities were suspended by means of pins through the os calcis and balanced traction. A second set of autografts were transplanted four weeks later to the now chronically ulcerated wounds. Six months following admission all the granulating surfaces were covered with grafts of autogenous skin.

Flexion contractures developed over the buttocks and the left popliteal space. These were treated by relaxation incisions into which autogenous grafts of skin were inserted.

The patient was treated with physiotherapy and was well rehabilitated when he left the hospital.

An interesting complication occurred to the father of the patient. Four hundred eighty square inches of thick-split skin had been taken from him, and he developed upper gastrointestinal bleeding presumed to be from a Curling's ulcer of the duodenum. Upon the second postoperative day he vomited 200 c.c. of coffee-ground material. He vomited

Fig. 21.—Homologous skin grafts from a white man transplanted to the leg and thigh of the patient who was treated with ACTH for twenty days (Case 3).

similar material intermittently for two days, in spite of the fact that he was allowed nothing by mouth. Stools were guaiac positive. The hemoglobin fell from 16.6 to 11.3 Gm. and the total proteins from 6.6 to 5.4. He was given 500 c.c. of whole blood. X-ray films of the esophagus and of the duodenal bulb taken at a later date showed no pathologic condition. His improvement was such that he was discharged sixteen days following the taking of the homografts.

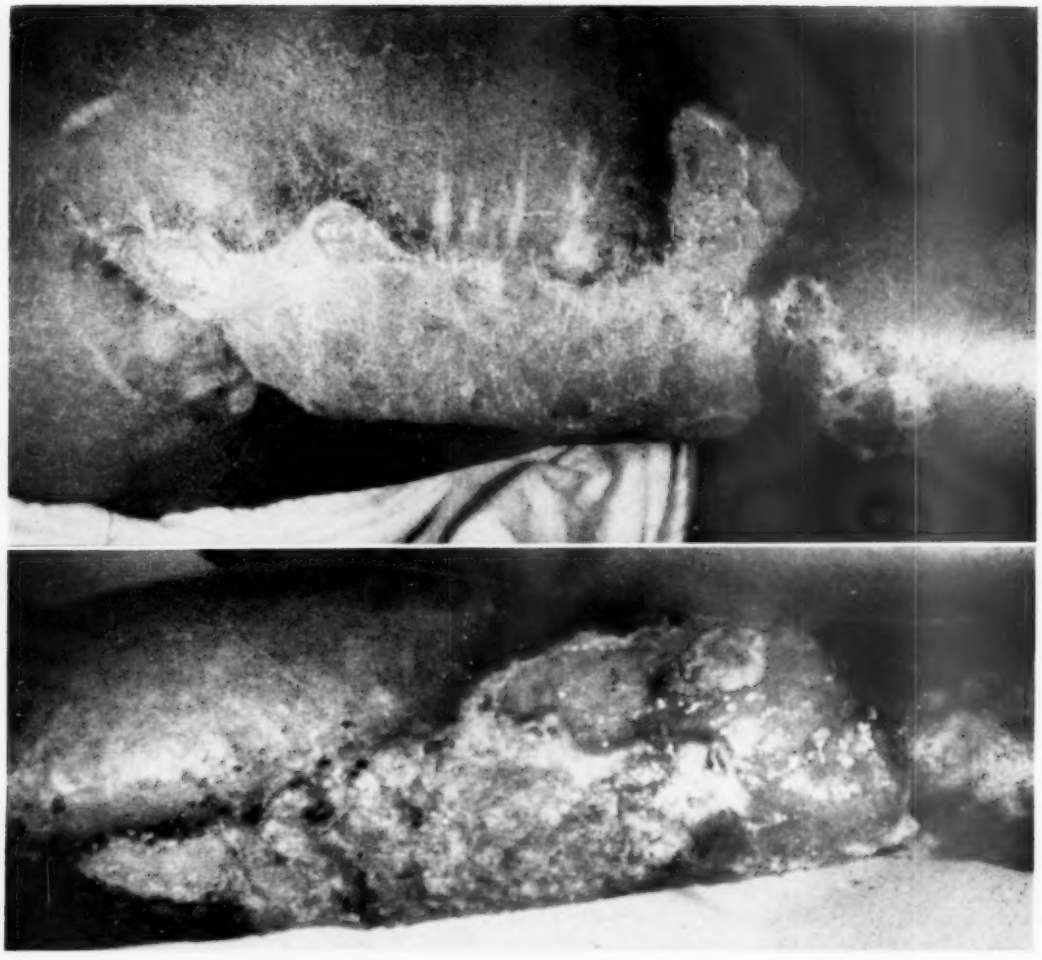
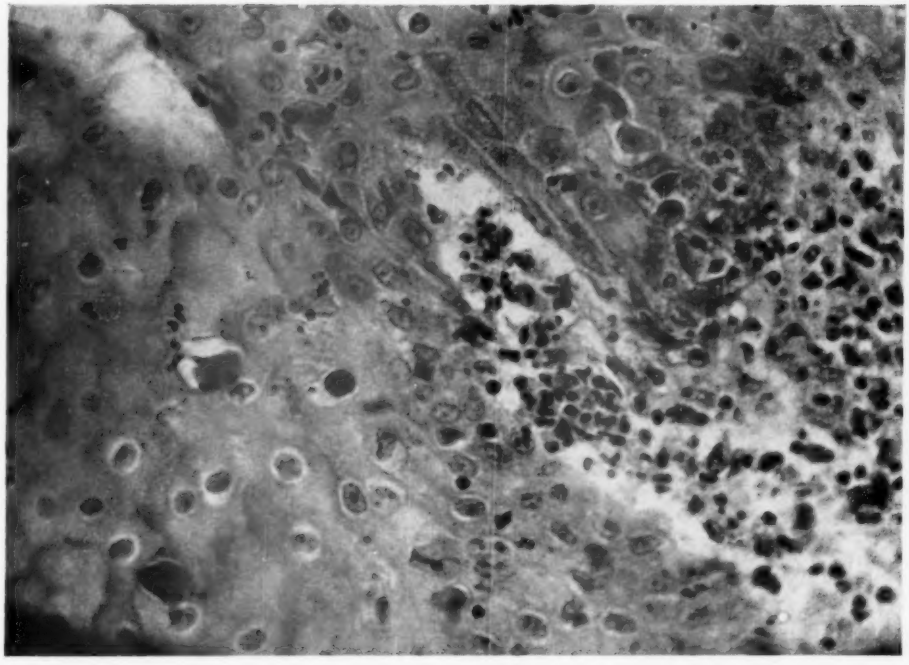


Fig. 22.—After the homografts had been tolerated well for one month, they became covered with an exudate and began to regress (Case 3).

Fig. 23.—The homografts of skin were removed and the wounds were covered with autogenous grafts of skin. The first of these was transplanted five days following the removal of the homografts. The major portion of these autografts was lost. Multiple thromboses of the recipient bed, as shown by biopsies, were believed to have been the cause of failure of the first set of autografts. Additional autografts were transplanted ten days later at a time when it was presumed that the vessels of the bed had become recanalized. These were successful (Case 3).



A.

B.

Fig. 24.—Biopsies of a homologous skin graft in the human being showing an acute and chronic cellular response to the homograft with thrombosis of some of the vessels in the field (*B*). It is felt that this thrombosis of the vessels of the recipient bed may have been the cause of failure of the autografts which were placed upon this bed five days later (Case 3).

CASE 3.—E. E., New York Hospital case No. 587661, *skin homografts as temporary coverage for large ulcers due to chronic infection; subsequent coverage of wound by autogenous grafts; failure of first set of autogenous grafts due to multiple thromboses of recipient bed of wounds initiated by the homografts; recovery following subsequent autografting of skin.* One year prior to admission a 31-year-old Negress slipped while working, causing an abrasion of the skin of the left leg over the tibial crest. To relieve the pain, the patient administered turpentine locally. Healing was delayed. Infection developed and tissue necrosis spread circumferentially about the leg. Ten months prior to admission a thick-split skin graft was applied in another institution. This was unsuccessful and the donor site on the ipsilateral leg also became infected. At that hospital, through an eleven-month period of time, the patient had been treated by multiple transfusions of blood, large doses of penicillin and of Aureomycin, and locally by a variety of measures including pastes, ointments, wet dressings, and exposure to the air. When she was admitted to the New York Hospital, both wounds were badly infected and exhibited deep cicatrization of their widely ulcerated bases. The wounds were covered with infected exudative crust (Fig. 19). The patient was malnourished and dehydrated. A lesion measuring 20 by 25 cm. extended around the left leg in annular fashion. The open lesion of the left anterior thigh measured 18 by 16 cm. There was flexion contracture of the left knee measured at twenty degrees. Biopsies of the wound margins showed only chronic ulceration. Bacterial flora of the wounds was as follows: hemolytic *Staphylococcus aureus*, gamma nonhemolytic Streptococcus, *Pseudomonas fluorescens*. Mazzini test was doubtful; Wassermann test was negative. The patient objected to another autogenous skin graft because of the previous spread of the infection to the donor site. She gave permission for a homologous skin transplant. Therapy with ACTH was started before operation for purposes of clinical investigation as to the value of this agent in the promotion of the survival time of the homologous skin grafts. Observation was made that the induration about the wounds seemed to diminish rapidly with therapy (Fig. 20). Twenty-five milligrams of ACTH was given every six hours. Five days after therapy was started with ACTH, homologous grafts from a white man were transplanted to the leg and thigh (Fig. 21). These grafts were tolerated well for about one month, when small areas of loss became apparent (Fig. 22). Soon the grafts were covered with exudate. Biopsy of the grafts at this time showed an acute and chronic cellular response. Small thromboses were present in the dermis and in the subcutaneous tissues. Thirty-seven days following homotransplantation the remnants of grafts were removed and the wounds were débrided. The survival time of the grafts, therefore, was no longer than in cases in which ACTH had not been used as an adjunct to homoplasty. Five days later autogenous skin grafts were applied to the granulating wounds. These grafts did not do well. The major portion of them was lost. It was necessary to apply autografts at two successive operations before the wounds were covered effectively (Fig. 23). In retrospect, the thromboses of the wound, shown on biopsy, and not unlike those observed in experimental animals, are believed to have been the cause of the failure of the first set of autografts (Fig. 24). The patient was discharged from the hospital with completely healed wounds four months after admission.[90]

SUMMARY

Widespread use of the word "graft" in the current literature in association with transplants of preserved tissues such as bone and blood vessels has prompted this review of the literature on homoplasty with a view to clarifying the definition of the term and evaluating the present status of homoplasty of specific tissues and organs. Distinction must be made between homovital and homostatic grafts. The former are those in which the tissue retains the anatomic stigmas of the donor while producing the physiologic or pathologic effect expected of the specific tissue. Only homografts of endocrine glands (parathyroid in the

human being) and of tumor (in experimental animals) can be classified as homovital grafts. Kidney is successful temporarily as a homovital organ transplant. All other tissues transplanted homoplastically in the human being eventually are replaced by ingrowth of tissue from the host.

Experimental observations in the development of the vascular pattern of homografts of skin in animals are reported upon. Detailed experiments in which various therapeutic agents have been used in attempts to block or limit the immune response of the recipient either by treatment of the recipient or the donor are reported. The significant observation in these experiments has been the early development with uniformity of multiple thromboses in the recipient bed to which the homograft of skin is transplanted. This appears to be the initial cause of failure of homografts. Limitation of this factor by specific therapy (Dicumarol, Benadryl, ACTH, and so forth) has prolonged the survival of homografts of skin only to allow for observation of a second barrier, namely, the failure of the development of permanent stromatization of the homografts. This appears to be due to an unexplained inimical state between recipient and donor.

Case reports are given in which the laboratory observations in animals have been sought for in human beings in whom homoplastic skin grafts have been used. In one case, that of a hemophiliac person, the factor of the development of thromboses in the wound to which homoplastic skin is transplanted was utilized practically to stop hemorrhage from a large open wound.

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FATE OF ESOPHAGEAL HIATUS HERNIA: A CLINICAL AND EXPERIMENTAL STUDY

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THE apparent discrepancy between the early treatment of esophageal hiatus hernias and other abdominal hernias has led us to an investigation of the course of small esophageal hiatus hernias. Whenever other abdominal hernias are discovered, whether symptomatic or not, surgical correction is advised. The early surgical repair of esophageal hiatus hernias has not been pursued in this country. The literature is replete with series of patients who have had surgical repair of hiatus hernias, but in most of these reports, the cases presented have been of patients operated upon because of serious complications. The patients have been critically ill in some instances. It is interesting to note that there is frequently a sentence or a paragraph, in most of the reports, stating that small or asymptomatic hiatus hernias should be treated conservatively (medically) or disregarded. It is also worthy of note that in the listings of principal indications for surgery in hiatus hernia, hemorrhage occurs as a single indication in about 20 per cent of the patients.[7-9] To wait until this occurs is to court disaster. A severely bleeding patient is a very poor surgical risk. It is with these facts in mind that a study was undertaken to determine the fate of small esophageal hiatus hernias which were discovered on roentgenologic gastrointestinal examination, and which were studied on more than one occasion. In addition, in order to study the ulcer diathesis-abetting factor of esophageal hiatus hernia, an experimental study was undertaken. It is the purpose of this paper to present these data.

MATERIAL AND METHODS

Clinical.—In order to study the size changes in esophageal hiatus hernias, the films and roentgenologic reports of 149 patients with hiatus hernias were reviewed from the files of the Ancker Hospital in St. Paul and the University of Minnesota Hospital. This review covered a period of eighteen years including 1953. The 149 cases studied were selected from about 6,300 roentgenologic gastrointestinal examinations. The criteria for selection of these cases were as follows: (1) There were at least two roentgenologic examinations at least one year apart. (2) Hernias measuring up to 6 cm. in diameter were classified as small hernias. (3) Hernias involving one-third or more of the stomach were classified as large hernias. Figs. 1 and 2 show a typical small and large esophageal hiatus hernia. The 149 cases were divided into two groups depending upon the length of time of roentgenologic follow-up from the first demonstration of small esophageal hiatus hernia. The first group of cases had roentgenologic follow-up from one to five years. The second

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group of cases had follow-up for six or more years. In addition to this, it should be mentioned that fifty-seven cases (44 per cent) in Group I had follow-up examinations in one year, and thirty-four cases (26 per cent) had follow-up examination in two years. To study the incidence of pathologic changes as observed in roentgenologic examinations in large esophageal hiatus hernias, the films and reports of sixty-one patients with large hiatus hernias were reviewed. Thirty-two of the sixty-one patients were not included in this survey because large hiatus hernias were present on the first roentgenologic examination.

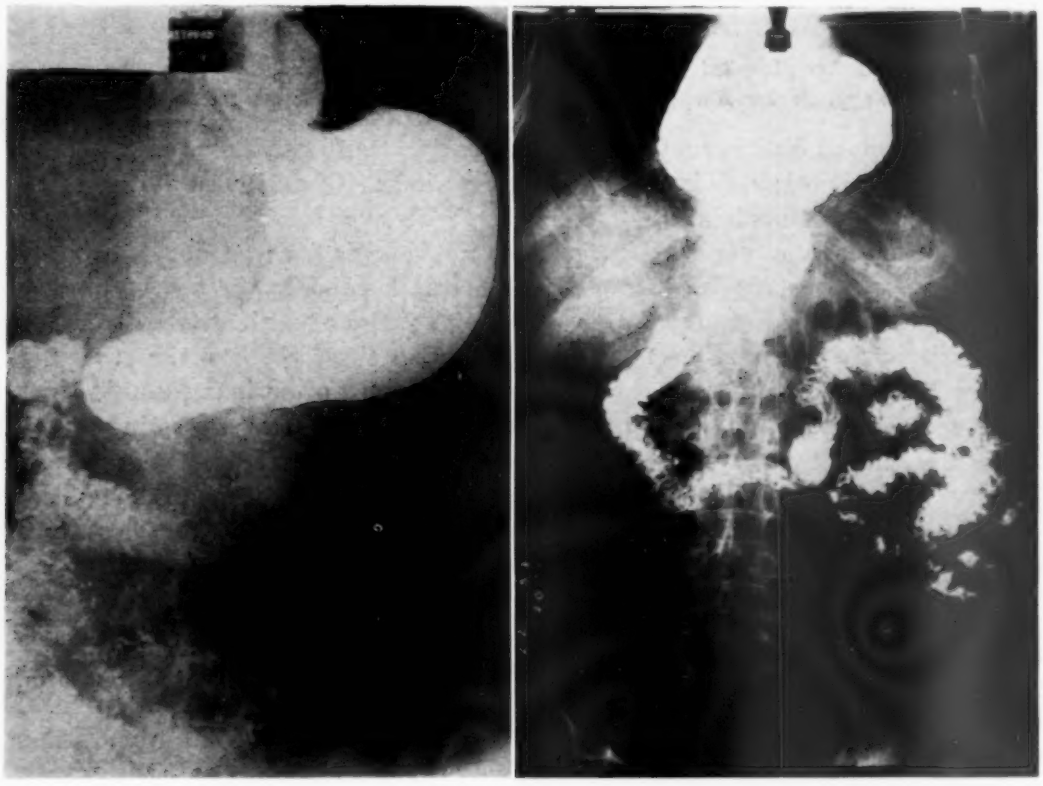

Fig. 1. Fig. 2.

Figs. 1 and 2.—Roentgenograms showing typical small (Fig. 1) and large (Fig. 2) esophageal hiatus hernias in patients.

Experimental.—In order to study the ulcer diathesis-abetting factor of esophageal hiatus hernia, the following experiment was conducted on dogs. Healthy adult mongrel dogs were divided into three groups. In the first group of animals an attempt was made to simulate the so-called paraesophageal or parahiatal type of hernia seen in human beings and described by Allison[1] and Sweet.[8] Exposure of the esophageal hiatus was obtained through a left thoracotomy in the ninth intercostal space. The esophagophrenic membrane was incised parallel to the left crus of the diaphragm for a distance of about 4 cm. The underlying fundus of the stomach was delivered into the chest, and the cut margin of the esophagophrenic membrane and adjacent diaphragm was sutured to the gastric wall with interrupted 0000 silk sutures. Compromise of nerves and blood vessels could be easily avoided. The second group of animals was prepared in a similar manner, differing only in that instead of opening the esophagophrenic membrane, the muscular crus of the diaphragm was opened in the direction of its fibers about 1 to 2 cm. lateral to its border. This was done to ensure normal position of the cardia or esophagogastric junction. In the third group of animals an attempt was made to simulate the so-called sliding type of hiatus hernia seen in the human being and also described by Allison[1] and Sweet.[8] In this

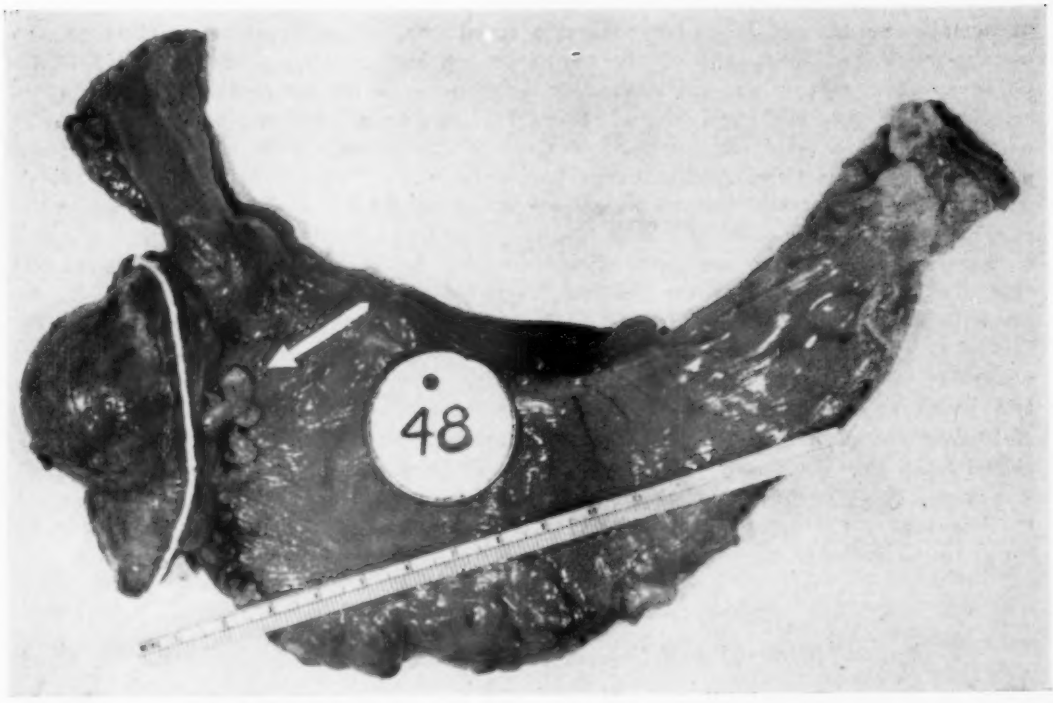

Fig. 3.—A small esophageal hiatus hernia in a dog.

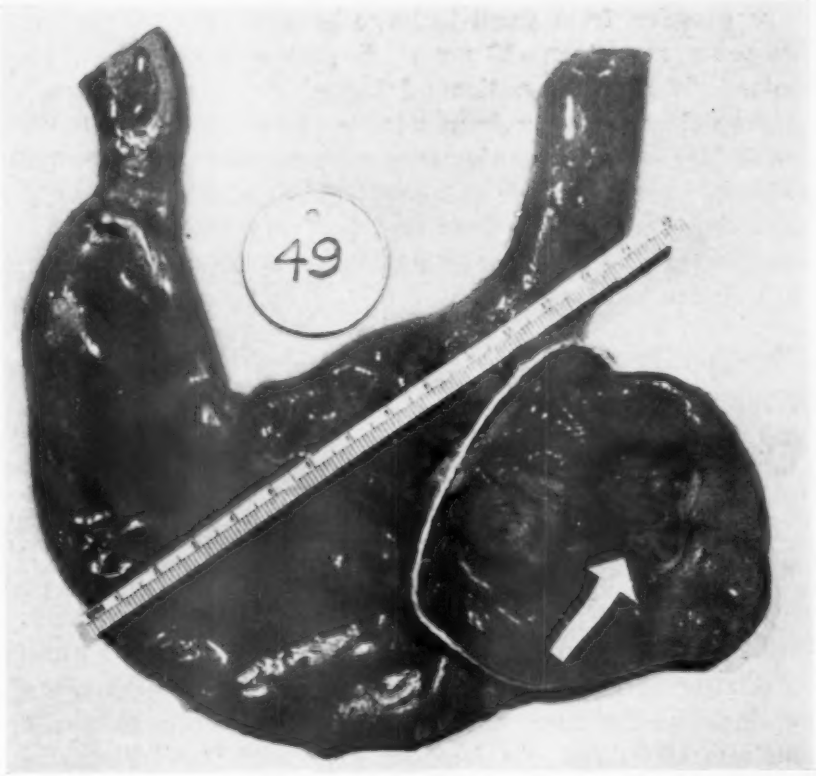

Fig. 4.—Perforation of a large esophageal hiatus hernia in a dog.

instance the entire circumference of the esophageal hiatus was opened at the diaphragmatic border of the esophagophrenic membrane. Slight upward traction on the esophagus allowed placement of the cardia or esophagogastric junction above the diaphragm. This position was maintained by suturing the herniated gastric wall to the circumference of the esophageal hiatus. Small hernias measuring 6 cm. or less in diameter and large hernias involving one-third or more of the stomach were made in each group of dogs except the third group. Large hernias were not feasible in the third group of animals since they would necessitate some sacrifice of the nerve and blood supply to the cardiac portion of the stomach. Following the operative procedures the dogs were allowed at least a three-week recovery period and in most instances one month's recovery. At this time those dogs which were vigorous, eating normally, and maintaining weight were given daily administrations of 30 mg. of histamine-in-beeswax mixture, as previously described.[6] During the course of histamine administration, the regular kennel food and water ration were continued. The batches of histamine were tested periodically on a gastric pouch dog. Histamine stimulation was continued until the death of the animal. Autopsies were made as soon after death as possible. In a few instances, dogs were sacrificed when they appeared terminally ill. The size and type of hernia were again noted. The locations of perforations, ulcerations, and hemorrhages were recorded. The autopsy specimens were photographed and fixed in formalin for microscopic study. Figs. 3 and 4 show, respectively, a small hiatus hernia and a large hiatus hernia with perforation.

RESULTS

Clinical.—The results of the roentgenologic survey of patients with small esophageal hiatus hernias are summarized in Table I. A total of 149 patients were followed by roentgenologic gastrointestinal examination up to eighteen years. Of this total number, twenty-eight patients (19 per cent) showed roentgenologic progression from small to large hernias. Of 130 patients followed one to five years, seventeen (13 per cent) showed progression from small to large hernias. Of nineteen patients followed six or more years, eleven (58 per cent) showed progression from small to large hernias. Of the sixty-one patients with large hiatus hernias who were studied for pathologic changes demonstrable by roentgenologic examination, seventeen patients (28 per cent) had complicating ulcers in the herniated portion of the stomach, esophagitis, or esophageal strictures singly or in combination. This observation is of great clinical importance.

TABLE I. NUMBER OF PATIENTS WITH SMALL ESOPHAGEAL HIATUS HERNIAS WHO DEVELOPED LARGE HERNIAS WITH THE PASSAGE OF TIME

YEARS OF FOLLOW-UP	NO. OF PATIENTS WITH SMALL HERNIA	NO. OF PATIENTS PROGRESSING TO LARGE HERNIA	PERCENTAGE
1-5	130	17	13
6 +	19	11	58
Total	149	28	19

Experimental.—The results of the experimental study are summarized in Table II, which shows the ulcer diathesis abetment in dogs with small and large esophageal hiatus hernias. Of fourteen dogs with large hernias, seven (50 per cent) died of perforated ulcer in the hernia. The average time of death from perforation was 15.8 days. Of fourteen dogs with small hiatus hernias, one perforated an ulcer in the herniated portion of the stomach. Of the remaining

seven dogs with large hernias, four were sacrificed and showed no evidence of ulcer in the herniated portion of the stomach. A perforated jejunum, a bleeding esophagus, and an unknown cause accounted for death in three animals.

TABLE II. ULCER DIATHESIS ABETMENT IN DOGS WITH ESOPHAGEAL HIATUS HERNIAS

NO. OF DOGS	HERNIA SIZE	NO. OF DOGS WITH PERFORATED HERNIA	AVERAGE TIME OF DEATH DUE TO PERFORATION (DAYS)	PERCENTAGE
14	Large	7	15.8	50
14	Small	1	20	7

DISCUSSION

The clinical data presented substantiate the view so often expressed by Harrington[4, 5] and others[2, 3] that esophageal hiatus hernia is a progressive disease as far as the size of the hernia is concerned. Of great clinical importance is the high incidence (28 per cent) of complications such as ulcer, esophagitis, and stricture occurring in large hernias as demonstrated by roentgenologic examination. Obviously serious complications such as bleeding or disabling symptoms, not noted in this roentgenologic survey, would increase the percentage of serious complications of large esophageal hiatus hernia. From the experimental data it can be concluded that small hiatus hernias do not abet the ulcer diathesis, but large hernias certainly do. Clinically small hernias progress to large hernias. The implication is that although not abetting the ulcer diathesis, the small hiatus hernia is potentially dangerous because of its tendency to enlarge.

CONCLUSIONS

1. One hundred forty-nine patients with small esophageal hiatus hernias were followed by roentgenologic examination for periods of time up to eighteen years. Of 130 patients followed from one to five years, seventeen (13 per cent) showed progression from small to large hernias. Of nineteen patients followed for six or more years, eleven (58 per cent) showed progression from small to large hernias.

2. Of sixty-one patients with large esophageal hiatus hernias, seventeen (28 per cent) showed roentgenologic evidence of serious complications such as ulcer, esophagitis, or esophageal stricture singly or in combination in the herniated portion of the stomach.

3. In dogs with experimentally produced esophageal hiatus hernias, the ulcer diathesis was greatly abetted by large hernias.

4. It is suggested that esophageal hiatus hernia is a potentially serious disorder. Patients with small esophageal hiatus hernias should be kept under constant observation, consideration being given to the early repair of these hernias should enlargement occur and before complications become manifest.

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DISCUSSION

DR. ROBNETT.—I would like to know if histamine used in dogs stimulates the production of ulcer.

DR. EDWARD L. HOWES (New York, N. Y.).—Did you say something about fusiform versus sliding-type hernia?

DR. MARK M. RAVITCH (New York, N. Y.).—How many patients with a small hernia were discarded because they could not be followed?

DR. SPRAFKA (Closing).—In reply to the first question, regarding histamine stimulation for the production of ulcer, we used 30 mg. of histamine-in-beeswax daily after the dogs had recovered from their operative procedures for about one month.

In regard to the second question, concerning fusiform and saccular type of hernia, we made no attempt to compare fusiform hernias with saccular hernias in our dogs. We were mainly interested in the relationship between hernia size and the occurrence of pathologic changes in the hernia. Sliding hernias far outnumber paraesophageal hernias in the human being, and sliding hernias are the more serious type. We feel that a large paraesophageal hernia is a bad actor, and the sliding hernia is worse.

In reply to the third query, about the number of patients with small hernias who were disregarded because of inadequate follow-up, I must admit that a number of patients were excluded for that reason but I cannot give you an exact percentage. Most of the patients excluded, however, had small hernias demonstrated relatively recently, that is, within the past five years.

EXPERIMENTAL COMPARISON OF PROTEIN AND FAT ASSIMILATION AFTER BILLROTH II, BILLROTH I, AND SEGMENTAL TYPES OF SUBTOTAL GASTRECTOMY

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IT HAS been conclusively established by both metabolism (intake-excretion) and weight studies that an appreciable percentage of patients exhibit some evidence of nutritional impairment after the Billroth II type of subtotal gastrectomy. In forty-three metabolism studies of thirty-five patients after a Billroth II type subtotal gastrectomy which were collected from the literature, there was impairment of fat assimilation in twenty-three of the thirty-five patients.[8] Likewise there was impairment of protein assimilation following Billroth II type subtotal gastrectomy in eleven of thirty-six collected patients. Also numerous writers have pointed out that a significant number of patients have difficulty in maintaining their weight after the Billroth II operation. In a recent report, over 80 per cent of the patients were stated to have difficulty in maintaining their weight after this type of gastrectomy.[17] Ivy, Grossman, and Bachrach[12] collected 864 cases from the literature in which weights before and after subtotal gastrectomy for peptic ulcer were compared. In 42 per cent of these 864 cases the postoperative weight was less than the normal preoperative weight.

Dissatisfaction with the nutritional status of patients after the Billroth II type of subtotal gastrectomy has caused some surgeons to utilize other methods of subtotal gastrectomy. Thus, the Billroth I type of subtotal gastrectomy has in recent years gained in popularity, particularly because of the work of Harkins and Moore, and has been utilized by an increasing number of surgeons because of the more nearly normal physiologic and anatomic arrangement which results when the residual gastric pouch is anastomosed to the duodenum. Also Wollaeger,[21] in fat excretion studies, found that in eight patients with a Billroth I type of gastrectomy, an average of 12.3 Gm. of fat per day was excreted in the feces as compared with an average of 19.9 Gm. of fat per day in ten patients with a Billroth II type of gastrectomy. (The extent of gastrectomy in the patients studied by Wollaeger was stated to be one-half to two-thirds of the stomach.)

Recently (1951) Wangensteen[6, 19] suggested segmental gastrectomy in which the pylorus and entire antrum are preserved and anastomosed to a small portion of the fundus of the stomach (5 to 10 per cent) as a type of subtotal gastrectomy suitable for the surgical treatment of peptic ulcer.*

In view of the importance of clearly establishing the comparative nutritional status following these different types of subtotal gastrectomy, an experimental comparison of nutrition with particular reference to protein and fat assimilation was made after the Billroth II, Billroth I, and segmental types of subtotal gastrectomy.

This investigation was supported by a research grant (G-3628) from the National Institutes of Health, Public Health Service.

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*More recently Wangensteen and his co-workers have introduced tubular gastrectomy with transverse gastroplasty.[13]

METHOD OF STUDY

Healthy mongrel dogs were subjected to Billroth II, Billroth I, or segmental types of subtotal gastrectomy. In each instance an estimated 75 to 80 per cent of the stomach was resected in accordance with the experimental findings of Wangensteen and co-workers that all three of these methods of subtotal gastrectomy provide adequate protection against histamine-provoked ulceration if 75 to 80 per cent of the stomach is resected.[2, 6, 14] In each instance the Hofmeister method of removing the lesser curvature portion of the residual gastric pouch was utilized. There were ten animals in each experimental group.

Two to six months after operation, metabolism (intake-excretion) studies were performed. Four individual seven-day metabolic periods were conducted in each animal. Thus, there were a total of forty seven-day metabolic periods in each experimental group of ten dogs. Likewise a total of thirty-eight seven-day metabolic periods were carried out in fourteen normal animals for controls. The animals were given constant daily diets calculated and chemically analyzed to furnish 80 calories per kilogram of body weight and containing 4 Gm. of fat and 5 Gm. of protein per kilogram of body weight. Any food not eaten was weighed and subtracted from the total intake. Fecal collection periods were demarcated with carmine markers. The feces for each period were weighed, homogenized in a Waring blendor, and fat and total nitrogen were determined on aliquot samples. Nitrogen was determined using Hoffman's photelometric modification of the Koch and McMeekin direct Nesslerization Kjeldahl micromethod.[11] Fecal fat was determined using the Soxhlet method.

After conclusion of the metabolism studies, the animals were placed on the normal animal hospital diet but were given excessive amounts and allowed to eat as much as they wished. Gastric motility was tested by feeding a barium-coated test meal of cooked horse meat, sugar, and a small amount of water. Serial x-ray films of the residual stomach were taken immediately after feeding the barium meal and at one-half-hour intervals for two hours. Animals were sacrificed at varying intervals ranging from four to seventeen months after operation. At autopsy the residual gastric pouch was removed and the capacity (volume) of the remaining stomach determined.

RESULTS

Protein (Nitrogen) Assimilation.—Graphic representation of the percentage of ingested nitrogen excreted in the feces during each seven-day metabolic period in the ten dogs subjected to Billroth II type of subtotal gastrectomy is presented in Fig. 1. The average percentage of fecal nitrogen excretion was 24.4 per cent with a range of 10.2 per cent to 46.4 per cent. Graphic representation of the percentage of ingested nitrogen excreted in the feces during each individual seven-day metabolic period in the ten dogs subjected to Billroth I type of subtotal gastrectomy is presented in Fig. 2. The average percentage of fecal nitrogen excretion was 19.3 per cent with a range of 7.3 per cent to 35.6 per cent. Graphic representation of the percentage of ingested nitrogen excreted in the feces during each seven-day metabolic period in the ten dogs subjected to segmental type of subtotal gastrectomy is presented in Fig. 3. The average percentage of fecal nitrogen excretion was 12.6 per cent with a range of 4.0 per cent to 26.0 per cent. The average percentage of fecal nitrogen loss during thirty-eight seven-day metabolic periods in fourteen dogs was 14.9 per cent with a range of 4.0 per cent to 35.8 per cent.

Fat Assimilation.—Graphic representation of the percentage of ingested fat excreted in the feces during each seven-day metabolic period in the ten dogs subjected to Billroth II type of subtotal gastrectomy is presented in Fig. 4. The average percentage of fecal fat loss was 27.7 per cent with a range of 8.7 per cent to 66.6 per cent. Graphic representation of the percentage of ingested fat excreted in the feces during each seven-day metabolic period in the

ten dogs subjected to Billroth I type of subtotal gastrectomy is presented in Fig. 5. The average percentage of fecal fat loss was 10.6 per cent with a range of 3.3 per cent to 22.8 per cent. Graphic representation of the percentage of ingested fat excreted in the feces during each seven-day metabolic period in the ten dogs subjected to segmental type of subtotal gastrectomy is presented

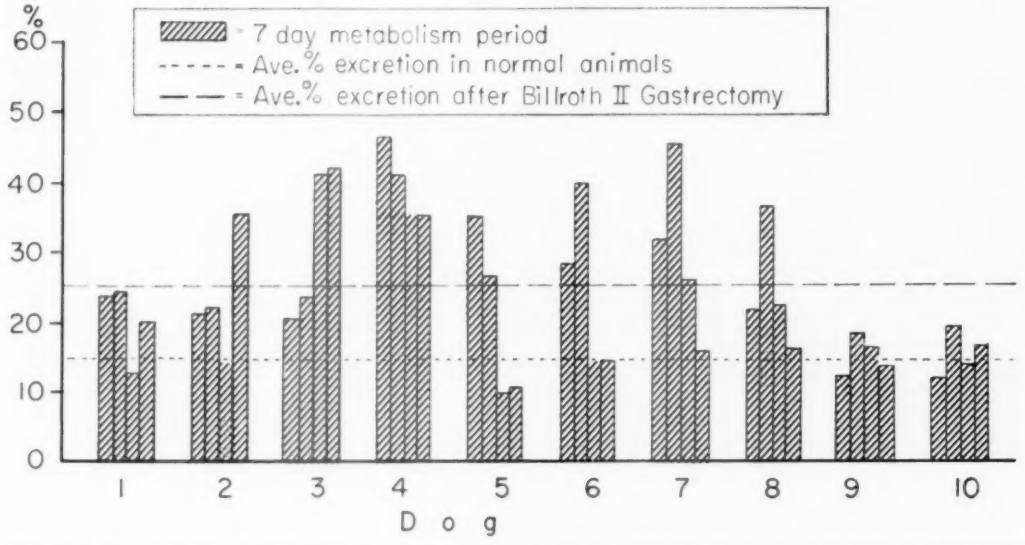

Fig. 1.—Percentage of ingested nitrogen in feces after Billroth II type subtotal gastrectomy.

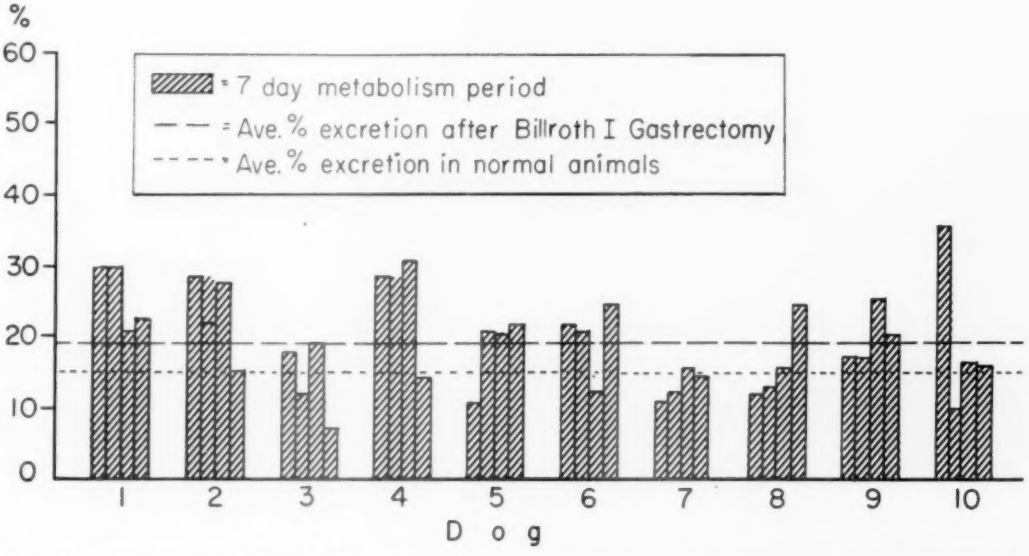

Fig. 2.—Percentage of ingested nitrogen in feces after Billroth I type subtotal gastrectomy.

in Fig. 6. The average percentage of fecal fat loss was 6.4 per cent with a range of 1.3 per cent to 13.9 per cent. The average percentage of fecal fat loss during thirty-eight seven-day metabolic periods in fourteen dogs was 4.9 per cent with a range of 1.0 per cent to 10.0 per cent.

Summary of Metabolism Studies.—Graphic comparison of the average percentage of fecal fat and nitrogen loss in experimental animals following Bill-

roth II, Billroth I, and segmental types of subtotal gastrectomy and in normal animals is presented in Fig. 7. The average fecal nitrogen loss following the Billroth II operation (24.4 per cent) is appreciably increased above the average percentage loss noted in normal experimental animals (14.9 per cent).

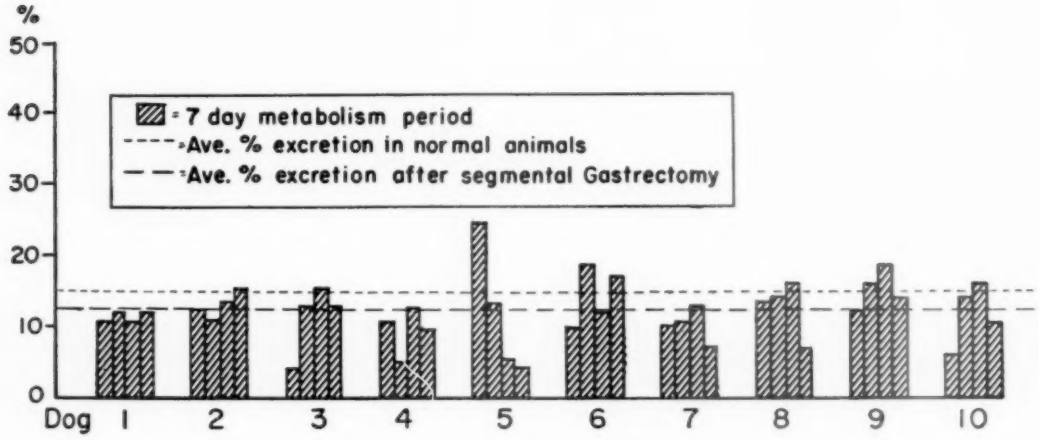

Fig. 3.—Percentage of nitrogen in feces after segmental type subtotal gastrectomy.

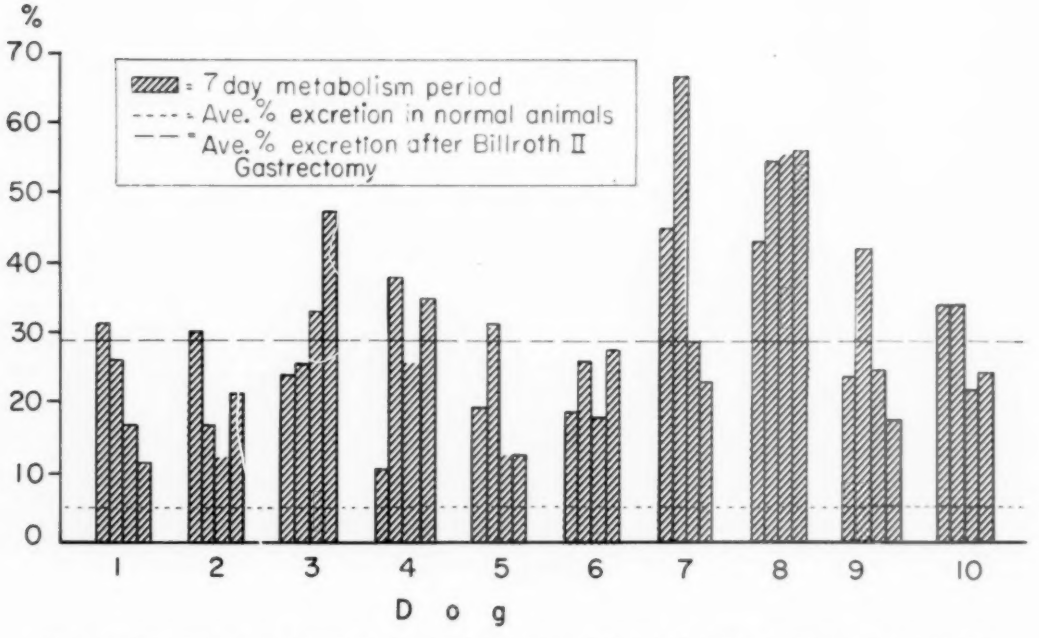

Fig. 4.—Percentage of ingested fat in feces after Billroth II type subtotal gastrectomy.

The average fecal nitrogen loss following the Billroth I type of gastrectomy (19.3 per cent) is less markedly increased and the average fecal nitrogen loss after segmental gastrectomy is not significantly different from the average excretion noted in normal dogs. The average percentage of fecal nitrogen loss is greater following Billroth II type subtotal gastrectomy (24.4 per cent) than following either Billroth I gastrectomy (19.3 per cent) or segmental subtotal gastrectomy (12.6 per cent).

The average percentage of fecal fat loss following the Billroth II type of subtotal gastrectomy (27.7 per cent) is markedly increased above the average percentage of loss present in normal animals (4.9 per cent). The average percentage of fecal fat loss after Billroth II gastrectomy is over five times greater

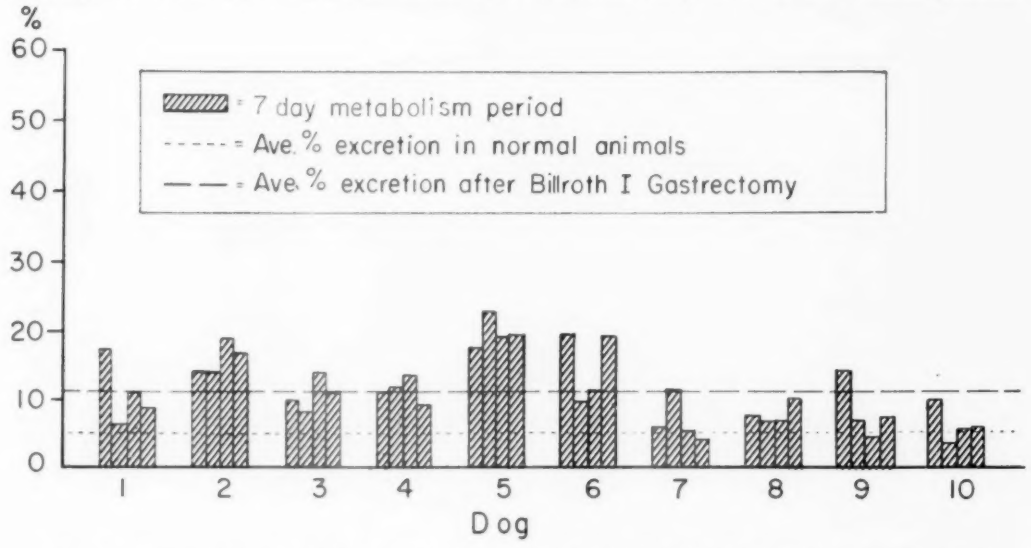

Fig. 5.—Percentage of ingested fat in feces after Billroth I type subtotal gastrectomy.

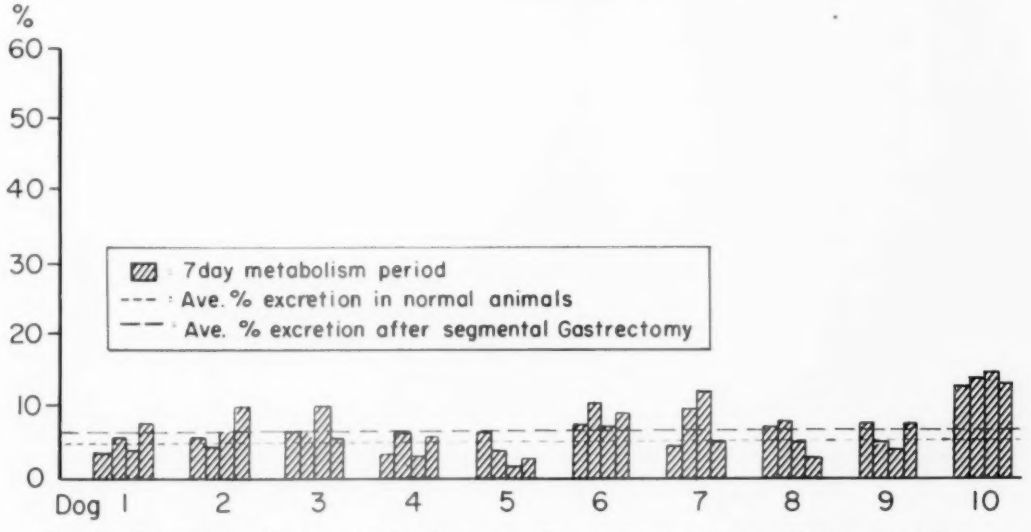

Fig. 6.—Percentage of ingested fat in feces after segmental type subtotal gastrectomy.

than that of normal animals. After Billroth I type subtotal gastrectomy the fecal fat loss is moderately increased (10.6 per cent) when compared with the average loss in normal animals, and the fecal fat loss after segmental subtotal gastrectomy is not significantly different from that noted in normal animals. Thus the efficiency of assimilation of fat is found to be much superior when the operation maintained the normal continuity of the gastrointestinal tract (Billroth I and segmental types of subtotal gastrectomy).

Weight Study.—Graphic representation of weight change after the various types of subtotal gastrectomy is presented in Fig. 8. Five of eight Billroth II

dogs for which weight records were available lost weight, two dogs gained weight, and one dog showed no weight change. Six of eight Billroth I dogs for which weight records were available gained weight, one dog lost weight, and one dog showed no weight change. Five of ten dogs following segmental

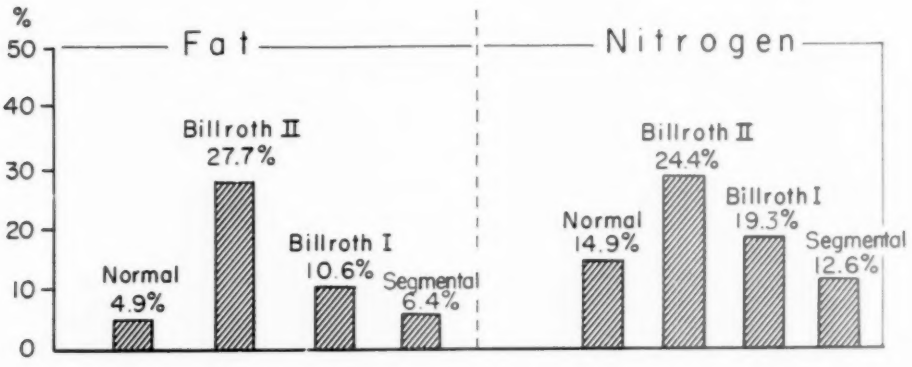

Fig. 7.—Average percentages of ingested fat and nitrogen in feces.

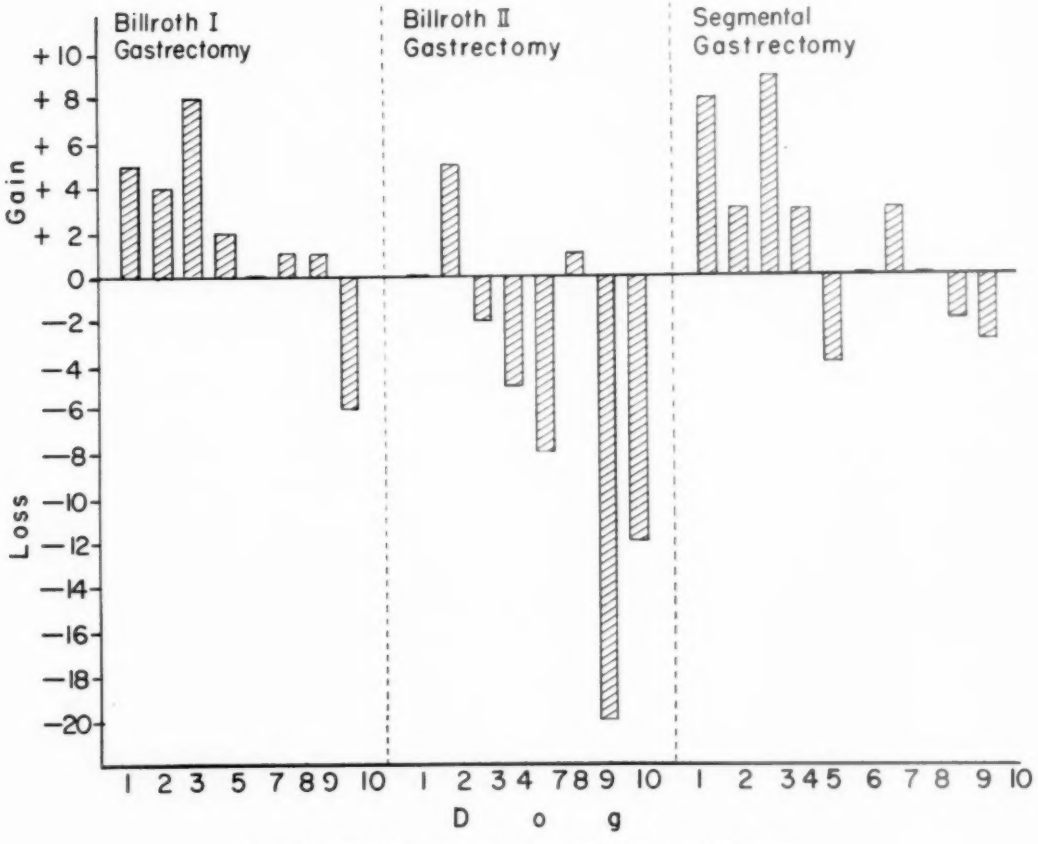

Fig. 8.—Weight change after subtotal gastrectomy.

gastrectomy gained weight, three dogs lost weight, and two dogs showed no weight change. All dogs were offered excessive amounts of food and permitted to eat as much as they wished. Thus on ad libitum diets the majority of ani-

mals subjected to Billroth I or segmental types of subtotal gastrectomy gained weight or maintained their weight while the majority of animals subjected to the Billroth II type of gastrectomy lost weight. In several instances the Billroth II animals were sacrificed because of severe inanition.

Possible Factor Which May Be Responsible for the Better Assimilation of Nitrogen and Fat After Billroth I and Segmental Types of Subtotal Gastrectomy.—

1. *Greater pancreatic secretion:* Annis and Hallenbeck[1] have reported a decrease in pancreatic secretion in response to a test meal in dogs following subtotal gastrectomy. Greater pancreatic secretion might be expected after a subtotal gastrectomy in which the food passes into the duodenum (Billroth I and segmental) rather than into the jejunum because of the known greater production of secretin[4, 5, 7, 9, 15, 20] and pancreozymin[10, 18] in the duodenum as compared with the jejunum. (Secretin and pancreozymin are secreted by the intestinal mucosa in response to the stimulation of food and in turn stimulate the production of pancreatic secretion.)

2. *Improved mixing of food and secretions:* There is a physiologic increase in secretion of bile and pancreatic juice following the ingestion of food. When a Billroth II type of gastrectomy is performed, some of the ingested food might be well down the intestinal tract before the increased amounts of pancreatic and biliary secretion reach the upper jejunum. Also when a Billroth II subtotal gastrectomy is performed, the pancreatic and biliary secretions would have to travel the entire duodenum and at least part of the afferent jejunal limb before making contact with the food. Accordingly, significant amounts of these juices might be absorbed before reaching the food. Thus, it would seem plausible to expect that there would be improved mixing of food and secretions following Billroth I and segmental types of gastrectomy where the ingested food passes into the duodenum, as compared with the Billroth II procedure where the ingested food by-passes the duodenum and enters the jejunum.

3. *Additional digestive and absorptive surface:* Following the Billroth II type of subtotal gastrectomy, the digestive and absorptive surface of the duodenum and proximal jejunal limb is probably essentially excluded from the processes of digestion and absorption. This is, however, probably not a factor of major importance in accounting for the improved assimilation of fat and nitrogen after the Billroth I and segmental types of subtotal gastrectomy.

4. *Gastric emptying time:* An experimental comparison of gastric emptying time (motility) was made by feeding a barium-coated test meal and noting the progress of the meal through the stomach by means of x-ray films immediately after ingestion of the meal and at one-half-hour intervals for two hours thereafter. Serial tracings were then made of the barium outline of the stomach pouch, and the surface area of these tracings was measured by use of the polar planimeter. The results of these studies are presented in Table I. The average percentage of barium remaining in the stomach after each interval of time was appreciably less in the animals subjected to Billroth II sub-

total gastrectomy when compared with Billroth I and segmental types of subtotal gastrectomy. No appreciable difference was noted between the Billroth I and segmental types of subtotal gastrectomy. Thus the residual gastric pouch appeared to empty more rapidly after the Billroth II operation.

TABLE I. GASTRIC MOTILITY AFTER SUBTOTAL GASTRECTOMY

TYPE OF SUBTOTAL GASTRECTOMY	NO. OF DOGS	% OF BARIUM REMAINING IN STOMACH			
		½ HR.	1 HR.	1½ HR.	2 HR.
Billroth II	8	60.4	39.3	20.6	5.1
Billroth I	9	70.0	50.2	30.3	13.6
Segmental	10	69.8	46.4	31.7	15.8

5. *Intestinal transit time:* The barium meal studies failed to establish any difference in intestinal transit time following the different types of subtotal gastrectomy.

6. *Gastric pouch size:* The capacities (volumes) of the individual residual stomachs of the experimental animals as measured at autopsy are listed in Table II. Despite the fact that an effort was made at surgery to keep the size of the residual stomach constant (75 to 80 per cent resection), reference to Table II indicates a considerable variation in the capacity of the residual gastric pouch. The average residual stomach capacity of eight dogs subjected to the Billroth II type of subtotal gastrectomy was 118 c.c. with a range of 37 to 230 c.c. The average residual stomach capacity in eight dogs subjected to Billroth I type of subtotal gastrectomy was 55 c.c. with a range of 37 to 135 c.c. The average residual stomach capacity in ten dogs subjected to the segmental type of subtotal gastrectomy was 93 c.c. with a range of 42 to 210 c.c.

TABLE II. CAPACITY (VOLUME) OF RESIDUAL STOMACH

BILLROTH II SUBTOTAL GASTRECTOMY			BILLROTH I SUBTOTAL GASTRECTOMY			SEGMENTAL SUBTOTAL GASTRECTOMY		
SUBJECT NO.	DOG NO.	CAPACITY (C.C.)	SUBJECT NO.	DOG NO.	CAPACITY (C.C.)	SUBJECT NO.	DOG NO.	CAPACITY (C.C.)
1	982	65	1	1962	75	1	1926	100
2	1788	70	2	524	38	2	3364	98
3	1790	55	3	6018	37	3	3908	66
4	35	37	4	786	—	4	2480	70
5	2151	—	5	2160	135	5	1928	140
6	2252	—	6	2333	—	6	1228	82
7	3947	170	7	2256	20	7	2345	73
8	2851	175	8	3117	19	8	1648	52
9	3594	145	9	3470	50	9	1260	42
10	4236	230	10	581	65	10	3828	210
Average (8 dogs)		118	Average (8 dogs)		55	Average (10 dogs)		93

Because of the variation in residual gastric pouch capacities in the different experimental groups, the possibility must be considered that the degree of impairment of assimilation of protein and fat after the various types of subtotal gastrectomy may be related to the residual stomach capacity. However, analysis of the data within experimental groups fails to reveal any correlation

between the individual gastric pouch capacity and the individual percentage of fecal excretion of either protein or fat.[3] Likewise, the average residual stomach capacity is greatest in the Billroth II group, yet the assimilation of both protein and fat is poorest after the Billroth II type operation. Accordingly, it does not appear that there is any direct relationship between residual gastric capacity within the limits in these studies (approximately 75 to 80 per cent resection) and the efficiency of assimilation of protein and fat. To establish further the presence or absence of a relationship between residual stomach capacity and fat and protein assimilation following Billroth II, Billroth I, and segmental types of subtotal gastrectomy, the metabolism studies of animals with approximately comparable gastric pouch capacities are compared. The residual stomach capacity of four dogs subjected to Billroth II gastrectomy, four dogs subjected to Billroth I gastrectomy, and five animals subjected to segmental gastrectomy is correlated with the average percentage of fecal nitrogen loss of these animals in Table III and with the average percentage of fecal fat loss in Table IV. For both fat and nitrogen losses, the same general pattern is present as in the comparison of the whole experimental groups. Accordingly, it does not appear that the metabolism results are related to the residual stomach capacities within the range limits noted in these studies.

TABLE III. PERCENTAGE OF INGESTED NITROGEN IN FECES AFTER SUBTOTAL GASTRECTOMY CORRELATED WITH RESIDUAL STOMACH CAPACITY (AVERAGE OF FOUR SEVEN-DAY METABOLISM PERIODS)

CAPACITY (C.C.)	BILLROTH II (%)	BILLROTH I (%)	SEGMENTAL (%)
50-55	32.0	22.1	12.5
65-70	20.3	19.7	11.2
	23.4	19.5	9.4
			13.7
135-145	16.0	25.7	11.9

TABLE IV. PERCENTAGE OF INGESTED FAT IN FECES AFTER SUBTOTAL GASTRECTOMY CORRELATED WITH RESIDUAL STOMACH CAPACITY (AVERAGE OF FOUR SEVEN-DAY METABOLISM PERIODS)

CAPACITY (C.C.)	BILLROTH II (%)	BILLROTH I (%)	SEGMENTAL (%)
50-55	32.4	10.4	5.2
65-70	20.5	17.8	6.5
	19.7	6.2	3.5
			7.2
135-145	27.3	10.8	3.2

SUMMARY AND CONCLUSIONS

1. Nutritional status was studied in experimental dogs following Billroth II, Billroth I, and segmental types of subtotal gastrectomy.

2. An average of 24.4 per cent of the ingested nitrogen (protein) was excreted in the feces of ten dogs subjected to Billroth II type of subtotal

gastrectomy, as compared with 19.3 per cent in ten dogs subjected to Billroth I gastrectomy, 12.6 per cent in ten dogs subjected to segmental gastrectomy, and 14.9 per cent in normal animals.

3. An average of 27.7 per cent of the ingested fat was excreted in the feces of ten dogs subjected to Billroth II type of subtotal gastrectomy, as compared with 10.6 per cent in ten dogs subjected to Billroth I gastrectomy, 6.4 per cent in ten dogs subjected to segmental gastrectomy, and 4.9 per cent in normal animals.

4. The majority of animals subjected to Billroth II type of subtotal gastrectomy lost weight on ad libitum diets while the majority of animals subjected to Billroth I and segmental types of subtotal gastrectomy gained weight or maintained their weight on similar diets.

5. The nutritional status of animals subjected to the Billroth II type of subtotal gastrectomy was markedly inferior to that of animals subjected to Billroth I and segmental types of subtotal gastrectomy.

6. The nutritional status after segmental type of subtotal gastrectomy was essentially normal. The nutritional status after Billroth I type of subtotal gastrectomy was inferior to that following segmental type of subtotal gastrectomy although the differences noted were not great.

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DISCUSSION

DR. HENRY THOMAS RANDALL (New York, N. Y.).—I would like to congratulate Dr. Everson on a very beautiful study and make some comments which have been of considerable interest to our group at Memorial Center in connection with this type of problem.

We have a number of patients who have had total gastrectomies for carcinoma of the stomach, and these patients more than ever emphasize the need of nutritional studies of this type to evaluate what can be done, if one must perform a total gastrectomy, to attempt to rehabilitate the patient nutritionally.

There are two observations in man which supplement this paper and which I would like to present. First is the observation by others, confirmed by our studies, that in man the amount of absorption of ingested fat is decreased by perhaps 20 per cent down to an absorption of about 70 per cent of ingested fat following high partial and total gastrectomies. The absorption of fat is linear with the intake, however. If a patient ingests 50 Gm. of fat a day, he will absorb 35. If he ingests 100, he will absorb 70. If he ingests 150, he will absorb 105, so that actually, although there is a deficit in the fat absorption, if the dietary intake can be increased sufficiently from a caloric standpoint, this need not necessarily be a problem. The same general observations are true as far as nitrogen is concerned. The average man loses 1 to 2 Gm. of nitrogen a day in his stool; totally gastrectomized patients lose 4 to 6 Gm. a day, but again the loss is proportional to the intake and if the intake can be high enough, this loss can be compensated.

Actually though, the patients and the animals, too, show nutritional deficits. I think that part of the explanation of this lies in the fact that these patients are incapable of taking in an adequate amount of food to cover the combination of their reduced absorption and nutritional requirements simply because of the fact that when they increase their amount of caloric intake, they run into the dumping syndrome. Studies of the dumping syndrome reveal that, in patients, the rapid action of enzymes when food is put directly into the jejunum may be somewhat of a hazard rather than an asset. Rapid hydrolysis of foodstuffs, particularly in patients with a total gastrectomy, appears to produce, through sudden fluid shifts, significant rapid reductions in blood volume which actually produce a shocklike pattern and all the symptoms that we associate with dumping.

I was very interested to see that this is borne out in Dr. Everson's experiment as far as his group's study of Billroth II is concerned because there you will note on the barium study that the emptying time of the stomach is most rapid. I can assure you that dogs are subject to dumping, because physiologic studies which we have been making demonstrate very well the fact that they do.

How can one add this up, then? If a patient is suffering from a nutritional deficit following gastrectomy, it is partially because of the fact that he is not absorbing nitrogen and fat as well as he would if he were normal, but also much of his difficulty may lie in a failure of intake because of fear of dumping symptoms. A dietary survey which we have made on patients with total gastrectomies has shown that the average daily caloric intake is less than 1,400 calories. The reason for this is that if they take in more food, they have marked symptoms of the dumping syndrome. I would suggest that in addition to our consideration of the absorption problem of whether a Billroth I or Billroth II or a sleeve resection is better, we might also consider the problem of what happens, and how rapidly, to food after it is ingested by any individuals in whom there has been major disorganization of the normal anatomy and physiology of the gastrointestinal tract.

DR. EDWIN H. ELLISON (Columbus, Ohio).—I rise to add my congratulations to Dr. Everson on this monumental piece of work. We also have been interested in this problem for some three or four years, and I would like to take this opportunity to point out several additional factors.

First of all, it should be remembered that gastric surgery, irrespective of type, may decrease the efficiency of fat, and in some instances of protein, absorption. A review of our data from recently completed metabolic studies in fifteen postgastrectomy patients suggests an inverse relationship between the efficiency of fat absorption and the amount of stomach removed. The best absorption in a series of eight Hofmeister gastrectomies was realized following a 70 per cent resection or less and averaged 79.9 per cent; a three-quarter resection decreased this value to 71 per cent, and removal of 85 per cent of the stomach dropped the efficiency to 61 per cent. The over-all average absorption efficiency for the Hofmeister-Polya group was 70 per cent, and the addition of vagotomy decreased the efficiency by 5 per cent. The best fat absorption was noted in the Billroth I vagotomy series and averaged 79 per cent in five patients.

Eleven of the patients included had lost weight with an average decline of 16 pounds since operation; five showed no change or had gained weight, and only one had equaled his minimal ideal. Meals were planned to contain the same food items and portions eaten by the patient at home. Once stabilized, the diet was held constant and balance studies were started.

Nitrogen equilibrium or a positive balance was realized in ten of the sixteen studies. The daily protein intake in this group averaged 95.6 Gm.; the daily caloric intake approximated 2,376. The importance of a diminished dietary intake was emphasized in six patients who failed to realize nitrogen equilibrium. In these instances, the daily protein intake averaged only 60.0 Gm. and available calories fell to 1,474 or almost one-half of the more favorable group. Such deficiencies, if persistent, undoubtedly played a considerable role in the unfavorable postoperative weight trends of these patients.

None of the patients showed normal fat absorption, and one of two demonstrated a reduction of the absorption efficiency to 70 per cent or below. Calorie loss due to fat in the stool ranged from 3 to 13 per cent of the total calorie intake and averaged 260 per day for the entire group. A parallel deficit in nitrogen absorption was also observed in nine patients, was greatest in those patients losing the largest amount of fat, and exceeded 3 Gm. per day in four instances.

Although this calorie loss may seem insignificant, it is continuous and represents a weekly total of 1,820 calories and a monthly waste of 7,280 calories. Since caloric deficiency manifests itself as a loss in body weight, a knowledge of the weight loss in pounds and the calorie equivalent of human fat permits an estimate of the extent of the deficiency. The average fat content of one pound of adipose tissue has been shown to be 395 Gm. or 87 per cent and its caloric equivalent approximates 3,759 calories.

The total caloric deficit represented by the average weight loss of 16 pounds is easily calculated, that is, $16 \times 3{,}750$. This value divided by the average number of weeks since operation represents the weekly caloric deficit which if persistent for sixty weeks would have resulted in a 16-pound weight loss. It follows that the measured calorie loss (1,820 calories per week) is more than sufficient to explain the weight trends and serves to illustrate the importance of even a minimal loss of nutrients in the stool in those patients whose dietary intake is restricted to maintenance. Unfortunately, the caloric intake will be limited to these levels in many cases as a result of disagreeable symptoms after eating, the incidence of which seems to be greater following the more radical procedures.

DR. WILLIAM W. SHINGLETON (Durham, N. C.).—I, too, would like to congratulate Dr. Everson. We have been interested in the possible effects of interruption of the vagus nerves in regard to external pancreatic secretion and its indirect effect on fat and protein absorption and digestion. We had previously found in patients that vagotomy appeared to have a depressing effect on external pancreatic secretion. We carried out experiments similar to Dr. Everson's in dogs on a standard caloric and protein intake; meas-

uring nitrogen output in the feces in a control group and a group having previous vagotomy and gastroenterostomy, we found there was no appreciable difference in fecal nitrogen output.

DR. FREDERICK P. ROSS (Fitchburg, Mass.).—Two years ago at the meeting of this society, Dr. Meadows and I reported on some seventy-odd patients who had gastric resections with the Billroth I method of repair, and we were very pleased with the way these people seemed to maintain their nutritional status and get back to work, and the almost total absence of the dumping syndrome.

However, in the time that has elapsed since then, we have abandoned this procedure completely for patients with duodenal ulcer because we have had a 20 per cent recurrence rate of ulcer which, after all, was the basic disease we were treating! We are still using it enthusiastically for patients with gastric ulcer, in which we have run into no difficulty. In our control group of those operations performed by the Billroth II technique, we still have no recurrence that we know about.

DR. C. D. SHERMAN (Rochester, N. Y.).—There are two factors in this problem that one might consider. One is the factor of re-establishing the normal alimentary route (that is, esophagus to duodenum, or esophagus to stomach to duodenum) versus an altered continuity (that is, esophagus to jejunum, or esophagus to stomach to jejunum).

The second factor, which may or may not be of some importance, is that of leaving a reservoir of sufficient size that large amounts of food are not dumped rapidly into the duodenum or jejunum.

I would like to ask the speaker his opinion of the second factor, in other words, if he feels that the amount of reservoir left is of any importance. I would like to ask him, second, his opinion of the substitution of a colonic segment (as has been done by Moroney in England). In patients who have had peptic ulcers, Moroney has substituted colonic segments between the stomach remnant and the duodenum and felt that his patients' nutrition was much improved thereby. Third, I wonder if he thinks that the substitution of an ileocolonic segment in patients who have total gastrectomies may make any difference in their nutrition. This has been done by Lee and others in recent years.

DR. EVERSON (Closing).—As was pointed out by the first two discussants, patients and experimental animals lose weight after subtotal and total gastrectomy not only because there is impaired assimilation of fat and protein but because frequently there is reduction of food intake. Dr. Ivy observed many years ago that even animals subjected to total gastrectomy would gain weight if they were fed 50 per cent more than their normal diet. The observations of the first two discussants have also been confirmed by the studies of Brain and Stammers in Great Britain.

We have studied a small number of experimental animals which have had colonic or jejunal segments interposed between the esophagus and the duodenum after total gastrectomy. Although these studies are few in number, they do not indicate, at the present time, that with the lengths of jejunum or colon used by us there is any superiority of fat assimilation, protein assimilation, or weight status when compared with animals in which the esophagus has been anastomosed directly to the duodenum. Thus, these few studies suggest that the main value of these colonic or jejunal pouches may be to permit more normal restoration of the continuity of the alimentary tract following total gastrectomy.

REPAIR OF ATRIAL SEPTAL DEFECTS IN MAN UNDER DIRECT VISION WITH THE AID OF HYPOTHERMIA*

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INTRODUCTION

HYPOTHERMIA makes it possible to operate within the open heart by the use of a simple technique. After the superior and inferior venae cavae have been occluded and the heart has emptied itself, the interior may be opened widely and examined.[1-3, 6, 8, 10, 12, 14] Of course, this uncomplicated way of looking within the bloodless heart may be used at normal body temperatures, but then the time period must be short, too short for practical value, or the central nervous system will be permanently injured. Hypothermia protects this sensitive system. When the body temperature is lowered, oxygen requirements are reduced,[4] so that total vascular occlusion at the heart may be sustained long enough to perform deliberate, anatomically precise operations within the heart under direct vision.

Thus hypothermia is one road by which a long-sought goal has been reached; of comparable interest are artificial heart pumps or heart-lung machines which offer another course to the same objective. It would seem that open intracardiac operations by either means will prove to be a definite advance over blind techniques, for a clear view in an uncramped working area improves the quality of the surgery performed in any part of the body. It is not yet possible, however, to say which method of performing open operations holds more promise of becoming a widely useful tool.

As it is now used, the system employing hypothermia has the disadvantage of not allowing as much time within the heart as is provided by a heart-lung machine. On the other hand, it does possess some noteworthy advantages, the most obvious of which are its simplicity and the fact that it permits a completely bloodless field. Coronary artery flow continues when a heart-lung machine is used, and this flow, which in the anoxic heart[13] and perhaps in the malformed heart[9] may be abnormally large, combined with some bronchial artery return through the pulmonary veins, must be continually removed from the operative field. With hypothermia, on the contrary, all circulation, including the coronary flow, is stopped while the heart is open. There is, furthermore, another advantage in addition to that of an unclouded field which is provided by complete interruption of the blood

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flow. Vascular occlusion, at the exit as well as the entrance channels of the heart, which is not possible with heart-lung machines, reduces the opportunity for coronary air embolism to occur.

A more important advantage than the bloodless and unencumbered field is the relative simplicity of the technique. Few people and almost no machinery are needed, thus limiting the number of human and mechanical points at which a lethal failure could occur.

Experimentally we have used this simple method to produce and repair intracardiac shunts similar to those found in man.[12, 16, 17] Atrial septal defects were studied first, and after learning to make and close them in dogs, we were able to use the same procedure in accomplishing the first successful repair of a congenital septal defect under direct vision.[12] Encouraged by this success we continued to use the method and have now operated upon eleven patients with atrial septal defects. Through this experience we have slowly learned enough about these defects and the operation so that we believe that it can be used safely to repair most of them.

TECHNIQUE

For clarity of description the procedure may be divided into three steps: cooling, the thoracic operation, and warming. In most respects the technique which has been used in man is similar to that which has been used for dogs.[12]

A. Cooling.—After anesthetic induction with Penthothal and curare, the trachea is intubated and a device for recording rectal temperature is placed. Electrocardiograph leads are attached and connected to a cardioscope or a direct writing machine. A large vein is cannulated, and the patient is then cooled by surface chilling with refrigerating blankets. These blankets contain a long rubber tube sewn between two layers of thin canvas, and they are cooled by an alcohol solution kept at 25° F. which is pumped through the tube. In Fig. 1 is shown a patient being cooled.

Enough anesthetic, decreasing in amount as the temperature falls, is given to prevent shivering, and after one to three and one-half hours the rectal temperature has reached a level of 29° to 31° C. (84.5° to 88° F.). Cooling is then discontinued. By this time hypothermia alone usually provides sufficient anesthesia, and the operation is started. Without additional refrigeration the temperature continues to fall, slowly reaching a low point between 26° and 28° C. (79° to 82.5° F.), where it remains for more than one hour, long enough to perform the intracardiac operation.

B. The Thoracic Operation.—In the first operations the chest was entered through the bed of the right fourth rib, but recently a transsternal incision has been used which allows a bilateral entry through both fourth intercostal spaces anteriorly (Fig. 2, *a*). This incision provides an excellent exposure of the heart and allows occlusion of both pulmonary roots while the heart is open.

After the chest has been opened, 4 to 8 c.c. of 1 per cent butacaine sulfate is injected into the pericardial sac. The azygos vein is ligated, and the superior and inferior venae cavae are isolated and encircled with double loops of heavy silk. In order to reach the inferior vena cava in man, it is helpful to open the pericardium down to its reflexion over the vein. This opening in the pericardium is continued upward to expose the heart widely. As the next step in preparation, both pulmonary ligaments are divided and narrow twill-tape loops are passed around the root of each lung, as has been suggested by Swan.[15] With these loops the pulmonary veins can be occluded while the heart is open, thus eliminating a slow inflow of blood which may otherwise partially obscure the field, especially in adults.

Before the cardiac inflow is occluded, the interior of the heart is carefully explored by inserting a finger through the right auricular appendage. Once the surgeon has a

Fig. 1.—An anesthetized patient is shown wrapped in the refrigerating blankets. The machine which cools and pumps the alcohol solution through the blankets is out of the picture.

satisfactory understanding of the pathology by this means, the wound in the auricular appendage is closed. Then, after the defect has been described to the assistants and a plan for its closure has been settled upon, the cardiac inflow is occluded by tightening the caval ligatures. After a few more heartbeats, the tapes around the pulmonary hila are tightened and the outflow channels are occluded by clamping both the aorta and pulmonary artery with a Satinsky vena cava clamp, one limb of which passes through the transverse sinus. This outflow occlusion is necessary in order to avoid air embolism, for with the clamp in place, air is kept from escaping beyond the aortic valve while the heart is open or while it is being filled during closure. Once this last clamp is closed (Fig. 2, *b*), a longitudinal incision is made in the right atrial wall and the blood remaining in the atrium is evacuated with suction, exposing the defect (Fig. 2, *c*).

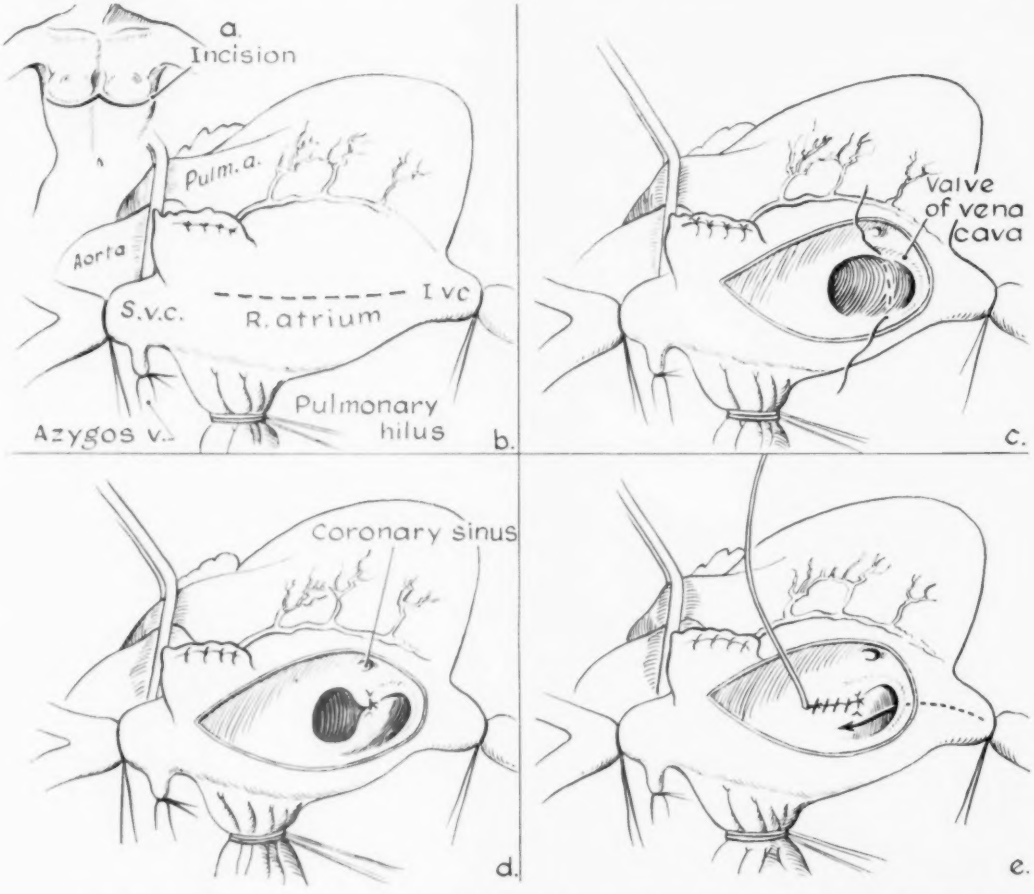


Fig. 2.—*a*, Chest incision through which the sternum is transected and both fourth intercostal spaces entered.

b, Following digital exploration through the atrial appendage, circulatory inflow and outflow, including both pulmonary roots, have been occluded and the atrium is about to be opened.

c, The atrium has been opened, exposing a defect of the membranous septum. Note how the anterior edge is continuous with the valve of the vena cava. The first stitch in the repair has been placed.

d, The first stitch of the repair has been tied, separating the defect from the orifice of the inferior vena cava.

e, The repair has been completed but the polythene tube used to fill the left heart with saline solution is still in place.

The defect is closed with a running stitch of 00 or 000 silk and one or two additional interrupted stitches (Fig. 2, *c and d*). As the last stitch is about to be tied, a small polythene tube is passed into the left atrium through the remaining crevice and just before

the tie is made, the left side of the heart is filled with saline solution, which is injected under pressure from a flask, thus washing out the air (Fig. 2, *e*). The polythene tube is removed and the right atrium is filled with saline solution as the wound edges are elevated

Fig. 3.—A patient is shown being warmed in the hot water bath which is kept at 45° C.

and finally closed with a Glover atrial clamp or a Satinsky clamp. Now the various occluding ligatures and the outflow clamp are removed and circulation is resumed, after which the atrial wound is sutured with a continuous silk stitch.

The total period of circulatory interruption has varied from 5 to 7¾ minutes. The heart beats sluggishly at first but soon regains its former vigor.

C. Warming.—During the operation the patient remains on the lower of the two cooling blankets, but now the alcohol solution flowing through it is heated, so that it reaches a temperature of approximately 110° F. while the chest is being closed. After the chest has been closed the body temperature is usually at its lowest level, the pulse is weak, and the blood pressure may be difficult to obtain. At this point the electrocardiograph may be needed to assure the staff that all is well.

To raise the temperature quickly, the patient is immersed in a hot water bath which is kept at 45° C. (114° F.) (Fig. 3). It has taken from thirty-five minutes to one and one-half hours to bring the temperature back to normal. As the body temperature returns to normal, the heartbeat becomes strong and the patient soon awakens.

RESULTS

Eleven patients with atrial septal defects have been operated upon during hypothermia. Summary information concerning them is contained in Table I. There were two operative deaths, and in a third patient (patient No. 2) the operation was terminated without performing the intracardiac procedure, thus leaving eight who have had the septal defects successfully closed.

TABLE I. PATIENTS WITH ATRIAL SEPTAL DEFECTS UNDERGOING SURGERY DURING HYPOTHERMIA (LISTED IN THE ORDER THAT THE OPERATIONS WERE PERFORMED)

PATIENT NO.	AGE (YR.)	SEX	LENGTH OF COOLING	LOWEST TEMPERATURE (°C.)	LENGTH OF REWARMING	LENGTH OF VASCULAR OCCLUSION (MIN.)	OUTCOME
1.	5	F	2 hr., 5 min.	26.0	35 min.	5½	Successful
2.	17	M	3 hr., 30 min.	24.5	1 hr., 10 min.	—	Ventricular fibrillation during cooling, repair not attempted, recovered
3.	46	F	3 hr., 13 min.	28.5	1 hr., 27 min.	7¾	Complete heart block postoperatively, died third postoperative day
4.	17	M	2 hr., 45 min.	28.0	1 hr.	7½	Successful closure, anomalous pulmonary vein remains
5.	10	M	1 hr., 48 min.	29.0	35 min.	5	Successful
6.	6	M	2 hr., 27 min.	27.5	—	8	Died during surgery—technical error
7.	21	F	2 hr., 24 min.	27.9	41 min.	5	Successful
8.	10	F	2 hr., 20 min.	27.0	1 hr.	5½	Successful
9.	19	F	2 hr., 5 min.	28.0	1 hr., 10 min.	6½	Successful, associated mitral stenosis
10.	35	F	3 hr., 22 min.	29.5	1 hr., 10 min.	5	Successful
11.	34	M	2 hr., 30 min.	27.5	1 hr., 35 min.	4¾	Successful

One of the two operative deaths was due to a technical error which led to a hemorrhage from the left atrium. We did not use finger exploration prior to the open operation in this case, and the accident was a direct consequence of our incomplete understanding of what proved to be a complicated defect.

The second death occurred suddenly on the third postoperative day in a 46-year-old woman (patient No. 3). Before surgery she was suffering from auricular fibrillation and congestive failure. At surgery, a septum primum defect was found and although a fairly good closure was obtained (Fig. 4), she developed a complete heart block with an idioventricular rhythm, which was doubtless a direct result of the repair. Since no other cause for her death was found at autopsy, we have attributed it to cardiac arrest.

Fig. 4A.—Photograph showing the repair obtained in a septum primum defect. The patient, No. 3, died on the third postoperative day.

One patient (No. 2) did not have his operation completed because spontaneous ventricular fibrillation occurred during the last part of the cooling period. After a rapid thoracotomy, his heart was successfully defibrillated with electric shock and massage. This occurred early in our experience, and although we might now proceed in a similar situation, we decided in this case, once the heart had recovered, not to go on with the repair. The heart in this patient was large and the beat was irregular with frequent ventricular extrasystoles before cooling, a heart which doubtless had an increased sensitivity to fibrillation. In the patients operated upon since this incident, we have used procaine-amide hydrochloride before and during cooling and there have been no more instances of spontaneous ventricular fibrillation during cooling.

Ventricular fibrillation has occurred, however, in three other patients (Nos. 4, 10, and 11) shortly after the repair was completed. In one case the fibrillation started just after the circulation was resumed and in two just

before. In all three, defibrillation was brought about promptly after electric shock* and massage were used, and the postoperative recovery was uneventful.

Postoperative recovery has, in fact, usually been untroubled but with perhaps more bloody drainage from the chest tubes immediately after surgery than is common following heart operations performed at normal temperatures. Otherwise the only notable postoperative complications among the patients with successfully repaired defect were one wound infection and a transient episode of auricular fibrillation which occurred in the 35-year-old woman (patient No. 10).

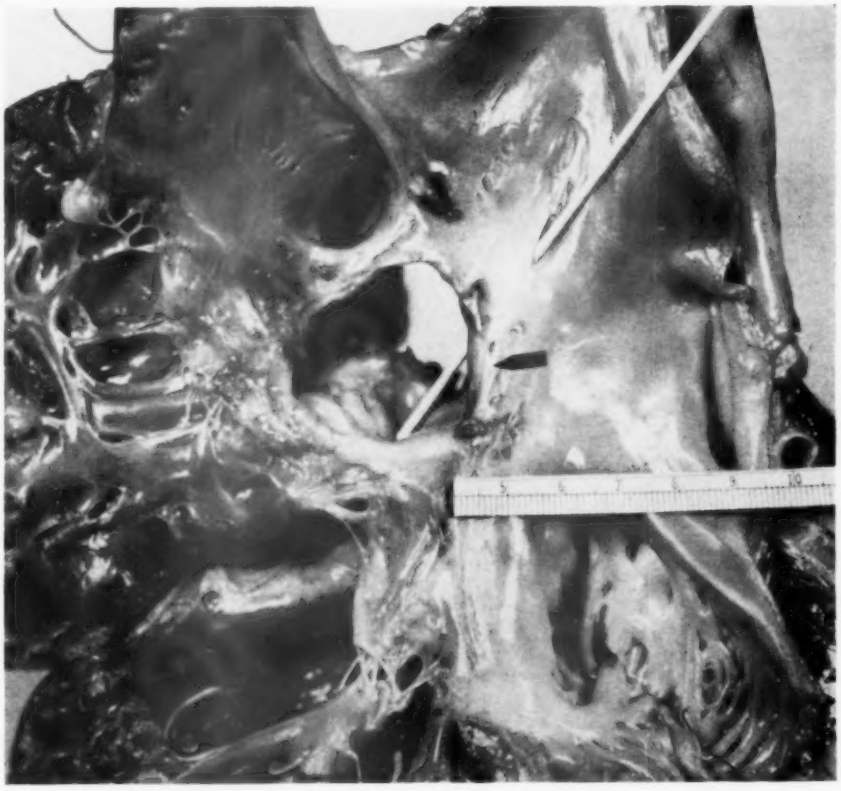
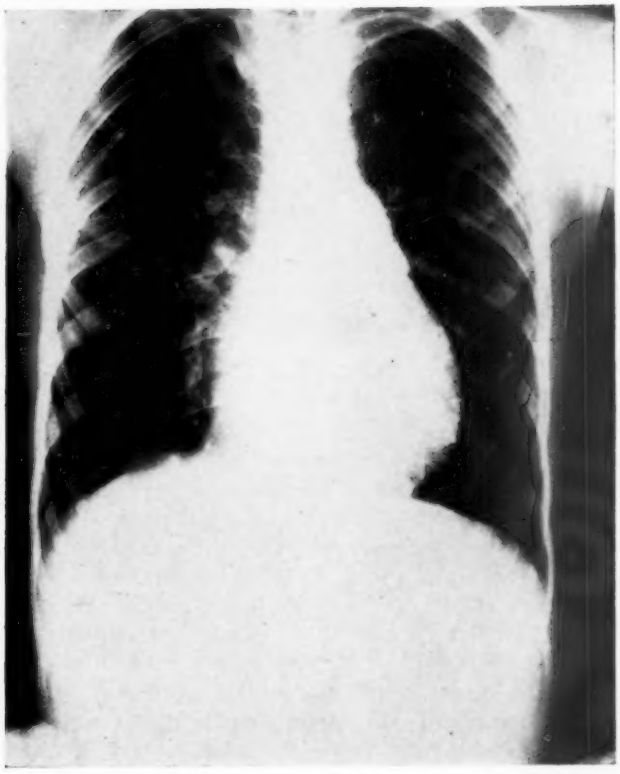


Fig. 4*B*.—The same defect but with the stitches removed to show the size and location of the defect.

Because of the relatively short time since surgery in most of these patients, maximum benefit has probably not yet been obtained, but nevertheless, the patients whose defects were successfully closed and who have had more than a few weeks to recover have all shown clinical improvement. X-ray studies also indicate improvement. Of the six patients more than one month since surgery, all except one show a decrease in heart size (Figs. 5 and 6), and the one exception shows no detectable change six weeks after surgery. Her operation has probably been curative, however, for postoperative catheterization studies suggest that she has a completely closed defect (patient 8, Table II). In most of the patients, reduction in cardiac silhouette is likely to be slow because of the prominent muscle hypertrophy which has developed in these hearts.

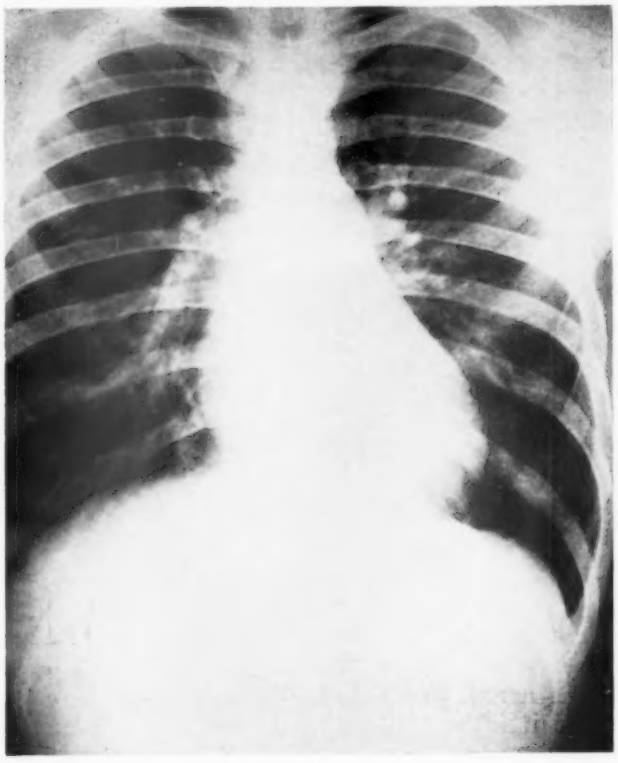
*Produced by an apparatus built with funds provided by the Greater University Fund, University of Minnesota.

A.

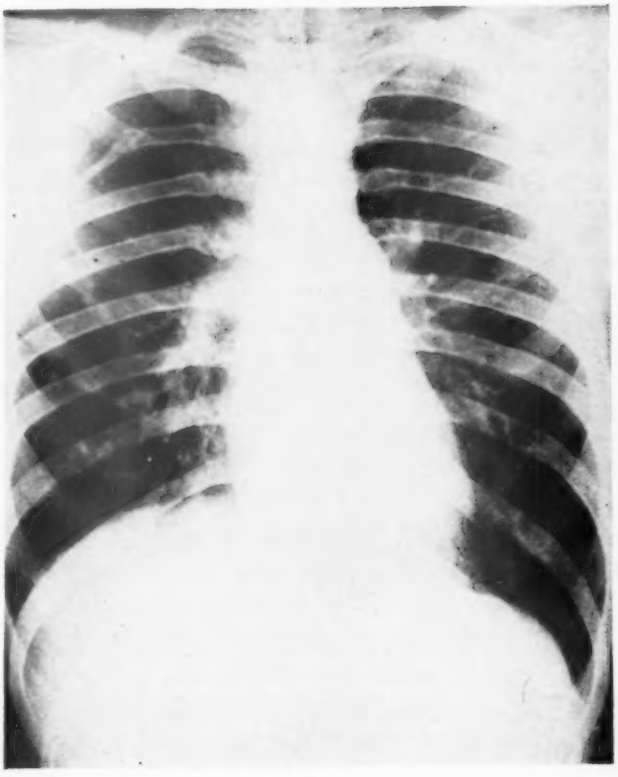


B.

Fig. 5.—Chest x-ray films taken prior to surgery (*A*) and eight months after surgery (*B*) in patient No. 5. Some reduction in heart size and in the pulmonary vascular markings may be seen.



A.



B.

Fig. 6.—X-ray films just before (*A*) and nine months after (*B*) surgery in patient No. 4. Again there is some reduction in the cardiac silhouette. This is the only patient who still has a left-to-right shunt (see Fig. 7).

TABLE II. RESULTS OF CARDIAC CATHETERIZATION BEFORE AND AFTER REPAIR OF ATRIAL SEPTAL DEFECTS (OXYGEN CONTENT IN VOLUMES PER CENT*)

PATIENT NUMBER†		VENA CAVA	RIGHT ATRIUM	RIGHT VENTRICLE	FEMORAL ARTERY
4	Before	10.7	15.4	15.8	17.2
	After	15.7	18.9	18.4	22.2
5	Before	13.6	16.0	16.8	17.6
	After	12.8	13.6	12.4	16.0
7	Before	12.0	16.6	16.4	17.6
	After	13.0	12.7	12.9	15.6
8	Before‡				
	After	12.1	13.0	12.9	16.0
10	Before	9.9	13.6	13.9	15.1
	After	11.9	12.7	12.5	16.1

*The significant comparison is between the vena cava and right atrial values at each catheterization. An increase of over 2.0 volumes per cent in the atrial value indicates a left-to-right shunt.

†Numbers correspond to the same number in Table I.

‡Preoperative catheterization was performed elsewhere, and quantitative data are not available.

Postoperative cardiac catheterization has been performed on five patients and, as is shown in Table II, four of them have no evidence of a shunt. The fifth patient (No. 4) still has a small shunt which seems to originate from an anomalous pulmonary vein entering the superior vena cava from the right lung (Fig. 7). His heart was not explored digitally before it was opened; at the present time it is improbable that we would overlook a similar complicating defect. Despite the residual shunt in this patient, the heart has decreased in size since surgery and it may not be necessary to perform another operation. Preoperatively the left-to-right shunt was estimated to be 10.3 L. per minute while it is now only 1.1.

In addition to the patients with atrial septal defects, three other patients, two infants 4 months of age and one child 4 years of age, have been operated upon. Each was considered preoperatively to have an atrial septal defect, but actually one of the infants and the 4-year-old child were suffering from persistent atrioventricularis communis (a common defect of both the atrial and ventricular septa), while the other infant had both a patent foramen ovale and a high ventricular septal defect. None of the three survived surgery. The two with persistent atrioventricularis communis were operated upon near the beginning of the series, and in each case the true margins of the enormous defect were not identified and a faulty and fatal repair was made. This error of identification could probably be avoided now since digital exploration has been added to the technique. The patent foramen ovale was closed in the third infant, but the far more serious defect of the ventricular septum was not recognized until autopsy.

DISCUSSION

Hypothermia.—Despite our concern, at first, that cold itself might be harmful for these patients, the deaths were not directly due to hypothermia. Although ventricular fibrillation, which was a complication in four of the patients, was doubtless caused, at least in part, by hypothermia, it was a surprisingly benign complication. Defibrillation was accomplished promptly in each case. In hypothermic dogs, too, when cooled to the temperature levels we have used in man, fibrillation has usually been reversible except when some additional serious complication such as coronary air embolism has occurred. Fortunately, we have had no instances of coronary air embolism

in the human patients and therefore can only surmise that this laboratory experience would be repeated in man. Even though we have not been able to prevent the occurrence of ventricular fibrillation in all patients, we have come to rely upon what seems to be an effective treatment, and hence this complication has not deterred us from continuing with the use of hypothermia.

Fig. 7.—Film taken during the postoperative catheterization examination in patient No. 4. The catheter is shown entering the right lung just above the right atrium. This has probably occurred through an anomalous pulmonary vein which enters the superior vena cava.

Correct Diagnosis.—Rather than any direct effect of hypothermia, the most serious hazard in performing these operations has been that of failing to make a precise anatomic diagnosis before attempting the repair. This failure has occurred both preoperatively and during the operation. Preoperatively the key to the diagnosis of an atrial septal defect has been the finding during cardiac catheterization of an abnormally high oxygen saturation in the right atrium. Yet catheterization findings may not help in distinguishing hearts deformed with anomalous pulmonary venous drainage, low septum primum atrial septal defect, persistent atrioventricularis communis, or an independent ventricular septal defect from those hearts which have a more easily repairable, high septum secundum defect of the atrial septum.

For the persistent atrioventricularis communis, there is at present no satisfactory method of repair, and it would be best to avoid surgery if an accurate diagnosis could be made. For some of the other defects mentioned, a repair may be possible; nevertheless, a precise diagnosis before surgery is still needed both as an aid in deciding whether or not surgery should be attempted at all and to help in planning for the specific operation if it is to be performed.

Digital Exploration.—Preoperative errors in making an exact diagnosis cannot yet be avoided, but it is usually possible to arrive at a correct inter-

pretation of the defect early in the operation, before the circulation is occluded. This is done by introducing a finger through the right atrial appendage for a painstaking exploration of the heart. At least in the adult hearts, a complete understanding of the defect can thus be obtained and detailed plans made for the actual repair. Hypothermia does not provide time enough for a long exploration after the heart is open, but this shortcoming is largely overcome by exploring with the finger. When the heart has finally been opened, the palpatory findings can be rapidly confirmed visually and the repair then started directly. To take further advantage of this exploration, we have planned, should an irrepairable defect be found, to abandon the operation at this point without adding the trauma of opening the heart. As yet, we have not taken this course.

Digital exploration was used in the last five patients listed in Table I, and in each case the operation was successful; it failed, however, in the one infant mentioned earlier to detect a high ventricular septal defect. These defects may be difficult to identify with the finger alone even in a much larger heart because they are found partially obscured by the medial leaflet of the tricuspid valve. Perhaps the use of a probe in addition to the finger would be helpful here.

Structure of the Defect.—Obviously, it is important during digital exploration to identify the edges of the defect and the relationship of these edges to the pulmonary vein, the venae cavae, and the coronary sinus. The right pulmonary vein, for example, may enter to the right of the posterior edge of the defect, as it has in two of our cases. When this variation is recognized, the stitches in the area of the vein should be placed in the atrial wall to the right of the vein orifice, ignoring the apparent edge of the defect, and thus bringing the vein orifice into the left atrium.

More common than this variation of the pulmonary veins has been an apparent malposition of the inferior vena cava (Fig. 2, *c*). In four of the last five patients, the inferior edge of the defect has appeared to be located to the right of the orifice of the inferior vena cava. If this false edge were used in the repair, blood from the inferior vena cava would be directed into the left atrium. Actually in these hearts there has been no true lower edge to the defect. The false edge inferiorly is the valvula venae cavae, which is continuous with the true edge anteriorly, as it is similarly continuous with the limbus fossae ovalis in the normal heart. When this characteristic of atrial septal defects is recognized, it is not difficult to close the lower part properly (Fig. 2, *c* and *d*). The first stitch is placed here, taking several bites to bring the anterior margin, the left atrial wall, and the posterior margin together before the remainder of the defect is closed.

There has been no need to use grafts in repairing even the larger defects. Although the heart is distended to begin with, it collapses when emptied and the margins of the defect come together easily. Then, once the repair is finished and the heart allowed to fill again, the same degree of distention does not return to strain the suture line.

Mitral Stenosis.—While examining the interior of the heart with the finger, most attention is directed to the anatomy of the defect, but it is also important to explore further. The mitral valve, particularly, should be examined. Although it is probably relatively uncommon, a concomitant mitral stenosis (Lutembacher's syndrome) may be encountered, as it was in one of our patients (No. 9). In this case commissurotomy was performed easily while the exploring finger extended through the septal defect into the left atrium.

Age of the Patients.—In view of the suggestion by other workers in this field that hypothermia should probably not be used for adults,[1, 5, 14] it is worth pointing out that, having operated successfully upon more adults than children, we disagree. Seven of our patients were over 16 years of age and three were over 30, yet among these adult patients there was only one death. It is not often necessary to turn patients down for this type of surgery because they are too old. On the contrary, if they are very young, surgery may not be indicated. This is not because infants withstand cold poorly, since they probably tolerate it better than adults, but because infants or young children with serious heart trouble usually have something more than a simple atrial septal defect, something which may not be repairable with present techniques.

Indications for the Operation.—It is valuable to know that adult patients with atrial septal defects can be safely subjected to surgical repair, for alarming symptoms often do not occur until adult life[7] and hence the diagnosis may not be made until then. When the diagnosis is made in adults, an operation should probably be performed, certainly if symptoms are present. Many children with the deformity are obviously in no urgent need of a surgical repair, but understandably, the few who have come to our attention have been sufficiently troubled, usually with recurrent respiratory infections, so that an operation was believed to be indicated. Indications for the operation are certain to be broadened in time to include more than just the patients who are already in difficulty. Ideally, when it can be demonstrated that the operative risk is small, all individuals with atrial septal defects should be treated surgically for, untreated, few of them enjoy a long life.[11, 18]

SUMMARY

1. In eleven patients with atrial septal defects, closure was attempted under direct vision during hypothermia. There were two operative deaths, in a third patient the operation was not completed, and in eight patients the operation was successful.

2. Ventricular fibrillation, a complication probably related to hypothermia, occurred during the operation in four patients, but defibrillation with electric shock and massage was obtained promptly in each instance.

3. Digital intracardiac exploration before the circulation is occluded has become an essential part of the operation. With it the anatomy of the defect may be comprehended before the heart is opened widely, and then even complicated defects can be accurately repaired in the time allowed.

4. At the present time the operation described is a safe and effective way of repairing all but the low or septum primum defects of the atrial septum.

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DISCUSSION

DR. HENRY SWAN (Denver, Colo.).—I certainly would like to congratulate Dr. Varco and his group on this very exciting work they are doing. We, too, have had some interest in the use of hypothermia for open heart procedures and we have now performed twenty-six such procedures with four deaths. Of these four deaths, three were in the group of nine patients on whom we operated who had interatrial septal defects. Of these three, two comprised 100 per cent of the patients who had the septum primum type of lesion. Both these patients, although they got through the operation all right, succumbed during the next twenty-four hours of a progressively enlarging and finally failing heart. I do not know—in our experience it has been very difficult to occlude or to close by direct suture these primum lesions without apparently doing some very serious damage to the heart which caused it to fail.

[Slide.] Our method of freezing is very simple. The house staff has recently taken me to task for this interest that we have in cooling patients. We just put them

in a tub of ice water, and they cool, I would gather, considerably faster than with the the cooling blankets. Our patients take from about fifteen minutes to as long as one hour to go into the same temperature range as that which Dr. Lewis has just described.

I just want to make one other comment. [Slide.] There has been a statement made that if a patient has severe pulmonary hypertension, then he is an unsatisfactory candidate for this operation. This is not necessarily true. Here is a 26-year-old girl who was unable to do her housework. She could not climb a flight of stairs and it was necessary for her mother to live with them to do the housework. You see the preoperative situation on your left. Note the tremendous size of the vascular markings in the lung field. The film on the right was taken two months following operation and shows some diminution in the heart size at this time and diminution in the visible evidence of pulmonary blood flow. It is now one year after operation. She now goes square dancing, and they have been able to send her mother back home, so that she seems to be getting along well.

The catheterization findings are critical in this decision.

[Slide.] Here was the pertinent thing, evidence of a big shunt of blood, left to right, giving a very large pulmonary flow. Notice that the right ventricle pressure was 100 mm. Hg preoperatively and the very gratifying fall in this pressure to normal after the shunt was closed.

We think, then, that although pulmonary hypertension may develop in these along the latter part of its course because of a tremendous flow which occurs on the right side, and that this may become fixed by pathologic changes in the pulmonary arterial bed or by thromboses occurring in the pulmonary arterial tree, as long as a big pulmonary blood flow is present, then there is no contraindication to close the defect just because of pulmonary hypertension. In fact, these people will benefit perhaps the most from such closure.

DR. W. G. BIGELOW (Toronto, Ontario).—Mr. Chairman, I think Dr. Lewis has established a definite milestone in first performing intracardiac surgery with the aid of hypothermia and following this work with the successful series of cases.

In thinking of hypothermia in relation to intracardiac surgery, it is important to differentiate between the adult and the child. Certainly infants and children appear to be much more tolerant of low body temperatures than adults. Thus intracardiac procedures which are expected to require more than a few minutes to perform will meet with more success in infants and children with our present state of knowledge.

Our group has not as yet attempted a closure of interauricular septal defects under direct vision with hypothermia. In adults we have had satisfactory results closing interauricular septal defects by closed methods using the hypothermia down to 30° C. as an adjunct to ordinary anesthesia.

In children, besides the obvious difficulty in diagnosing a pure septal defect in infants and young children, our cardiologists feel that from their concept of the natural life history of interauricular septal defects in children, a serious-risk operation is not warranted in the majority of cases. However, perhaps some of the results we are seeing now may influence that opinion.

If I may be permitted just for a moment, I would like to make some general observations regarding hypothermia since we have been interested in this subject for some time. We have been using hypothermia as an adjunct in the serious-risk patients for cardiac surgery such as mitral stenosis with chronic right heart failure with satisfying results. In cooperation with Dr. Mustard and Dr. Keith at the Hospital for Sick Children, hypothermia has been used both as an adjunct for standard operations upon the cyanotic group of cases and also as a means of performing intracardiac surgery under direct vision.

At the present time there is a lower temperature limit to which children can be safely cooled and for that reason a limit to the period in which the circulation may be

interrupted and direct vision procedures carried out. As you look at the congenital cardiac anomalies which may be repaired surgically, you have one large group of cases, including transposition of great vessels and tricuspid atresia, of patients who usually die in the first year of life. There is a second large group of interventricular septal defects with and without an overriding aorta. Then there are the two somewhat less complicated defects, namely, pulmonary stenosis and interauricular septal defects. As we all know, hypothermia has been applied to these latter conditions for the reapir under direct vision, and only time and a careful follow-up of results will determine the value of this.

Our own personal excursion into the use of hypothermia for intracardiac surgery has been in the first group of children, those who are expected to die within the first year of life. We have performed intracardiac procedures upon three such patients at 20° C. body temperature. Their circulation has been occluded for periods up to twenty minutes with sustained heart action, and all were revived to normal body temperature. None of the three has survived, principally because of technical difficulties in handling these more complicated lesions. We have been pleased with the effect of hypothermia and our ability to exclude the heart from the circulation for periods with retained cardiac action.

Actually, one of the difficulties has been a very practical one. In this first group of cases the heart is usually so large that there is no room for the surgeon to work in the chest cavity, and attempts to do so partially embarrass the heart.

The future of hypothermia may lie in combining extracorporeal circulation and hypothermia or may not come until there is a better understanding of the fundamentals of hypothermia. We must learn why adults cannot be cooled to as low a temperature as children and also why hibernating animals are able to withstand such very low body temperatures. With our studies of hibernation in the last few years, we are attempting to throw light on this subject.

I might say in closing that I think Dr. Lewis and Dr. Swan have shown excellent results in their clinical application of hypothermia, which is still so new.

DR. ROBERT E. GROSS (Boston, Mass).—This has been a brilliant display by Dr. Lewis, Dr. Varco, and Dr. Taufic. We are certainly all very grateful to have the privilege of hearing this presentation today.

I have had little experience with hypothermia. Our efforts in the field of attempting to close interatrial septal defects have been by other methods. There have been twenty-eight such attempts with eight fatalities and twenty survivors. We have approached the problem as follows:

Opening through the right chest, putting a finger in the auricular appendage, and exploring the interior of the atrium, one can determine rather accurately what is being dealt with. If the defect is posterior and not too large, we prefer to use some sort of a closed technique, either a Bailey atrioseptopexy or a modification thereof, by bringing the side wall or the back wall of the auricle to the anterior edge of the septal defect by interrupted sutures. If we find that the opening in the septum is more forward or is further downward, or is very large, we prefer not to attempt such closures, but prefer to put a rubber "well" onto the auricle and operate through that avenue. About one-half of our operations have been performed by the "closed" methods and one-half by the "well" procedure. In those cases where a "well" has been used, one-half of the septal openings have been closed by direct suture and one-half by the onlay of a thin sheet of polyethylene.

As far as drugs are concerned in the preparation of these people, and the maintenance of them during operation, our thoughts are as follows: We have abandoned pronestyl entirely. We have felt that in some individuals the drug gave such a suppression of cardiac action that there was a very disturbing fall in peripheral pressure. Digitalis I am not too sure about; in some cases it seems to help and in others it does not. We have little faith in it. We have come to use quinidine almost routinely and rely on it quite a bit for preventing, or reducing, cardiac irregularities.

As far as the results of operation are concerned, there are many factors in evaluation of patients. It is possible to get a brilliant result by closing of the shunt, but there are some patients (particularly in the older group from 35 to 50 years) who have not done too well following treatment of their septal defect, in spite of the fact that I am quite sure they had complete closures. These are individuals who before operation had cardiac irregularities (fibrillation, runs of auricular flutter, frequent extrasystoles, or a wandering pacemaker with complete dissociation of the auricular and ventricular beats). Such irregularities do not always straighten out magically when you close the septal defect. One is either dealing with a heart which has a defect in the conduction mechanism or else there is a heart which is tired from the great burden it has carried for several decades. In some of the older patients it takes a good deal in way of observation and medical management over a stretch of several months (quinidine, digitalis, low-salt diet, and so forth) to get them rehabilitated.

DR. WILLIAM H. MULLER, JR. (Los Angeles, Calif.).—I too would like to congratulate Dr. Lewis on this fine work. Although we have been interested in using hypothermia in cardiac surgery, we have not used it with vena caval occlusion for the closure of interauricular septal defects. Certainly a visual method is better. However, we have employed the method which Dr. Gross devised, in most instances, because it gives a great deal more time to explore the interior of the auricle. The problem of air emboli is eliminated, and in older adult patients we have been afraid of the development of ventricular fibrillation following the vena caval occlusion. Three of our patients were over the age of 40 years, the oldest being 45.

We have operated upon fourteen patients with interauricular septal defects, and two deaths have resulted. The atrial well has been used in all except one patient, 22 years of age, who had rather high pulmonary hypertension with a pressure of 80 mm. Hg in the right ventricle. We did not think that she would tolerate the well, and therefore used the Bailey technique. In one other patient we encountered a septum primum and sutured a nylon plastic patch over the defect on three sides, but could find nothing between the two valves to anchor it below. We thought that the patch would substantially reduce the shunt and benefit the patient. She progressed moderately well for about one week and then developed severe heart failure, so that about three weeks after the operation we reapplied the well and removed the plastic patch, which had been moved to the right by the high left auricular pressure so that it partially covered the tricuspid valve. She has now returned to her original preoperative status. We have not used plastic prostheses in any other patients, but have been able to approximate the edges of the defect with sutures.

[Slide.] This slide demonstrates pressure changes before and after the defect is closed. As one would expect, there is a drop in right auricular pressure and a rise in the oxygen saturation. There is likewise a drop in the right ventricular pressure and a slight rise in the left auricular pressure. Blood volume determinations which have been performed on some of these patients show a significant decrease in blood volume after operation.

DR. LEWIS (Closing).—I would like to thank the various discussors for their stimulating comments and comment in turn on a few of the things mentioned. First of all, I want to reiterate that we feel that hypothermia is not particularly dangerous for older patients. Most of our successful operations have actually been in the adults rather than in the infants or children. The oldest patient we have operated upon during hypothermia was a 72-year-old man who withstood the hypothermia well for a complete resection of the right lobe of the liver. He did, however, die three weeks after operation because of a late infection within the abdomen. This could not very well be attributed directly to the hypothermia.

As far as the risk of operating on people with irregular hearts, I would agree with Dr. Gross that the risk is greater and the results may well be poorer. There are only

two patients we have operated upon who had extrasystoles and gross irregularities. One was the 46-year-old woman who died and the other was the young boy who developed spontaneous ventricular fibrillation. Regarding indications for surgery, I agree with Dr. Gross again, for we feel that the operation usually is not indicated for young individuals.

One other point I would like to make concerns the complexity of some of these defects. First of all, the commonest confusing aspect is the position of the valve of the inferior venae cavae. In addition, three of our patients have had anomalous pulmonary vein drainage, which must be corrected during the repair by making a new margin rather than using the apparent margin of the defect. All these complexities impress us with the probable importance of using a direct open approach rather than a blind technique. These complex defects are probably easier repaired by direct approximation with sutures than they would be by grafts.

Finally, I would like to emphasize the importance of follow-up catheterization studies as the best criteria of the effectiveness of closure either by blind or by open techniques.

FACTORS CONTRIBUTING TO SUCCESS OR FAILURE IN THE USE OF A PUMP OXYGENATOR FOR COMPLETE BY-PASS OF THE HEART AND LUNG, EXPERIMENTAL AND CLINICAL

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FUTURE progress in the surgical correction of endocardiac disorders, as in other branches of surgery, appears to depend upon attainment of techniques for safely opening the heart to give adequate exposure for unhurried careful work. This problem has been attacked fundamentally from two angles, in some instances with considerable success. On one hand, Bigelow[1] and others[23, 31] have studied the possibility of temporarily obstructing the circulation by the use of hypothermia to lower the metabolism of vital organs. Thus, temporary cessation of circulation apparently does not damage them, yet the method has the disadvantage of time limitation. On the other hand, under the impetus of work by Gibbon,[11] Dennis,[7] Clark,[3] and many others, another experimental approach to cardiotomy has been that of sidetracking the blood stream around the heart and lungs while clamps on the great veins prevent blood from entering the cardiac chambers. In pursuit of the latter course, a type of "large bubble" oxygenator has been evolved with which seventy-four animals were perfused while the heart and lungs were not functioning for periods ranging from twenty-five to sixty-two minutes. It is not with these oxygenators themselves that we are primarily concerned, for they have their limitations and defects. But more important are observations on the forty animals which survived and the thirty-four which died. The purpose of this paper is to compare the observations made on those which lived with observations made on those which died and to present an analysis of the physiologic factors which contributed to the success or failure in these experiments. Finally, three patients, all desperately ill with cardiopulmonary lesions, were perfused in an effort to cure them. With the experimental results in mind, these cases are reviewed in an attempt to determine wherein success or failure was achieved.

Pumps have been used to substitute for one or both sides of the heart since Dale and Schuster[6] described their apparatus in 1928. Since then a number of surgical investigators have studied the possibility of applying this principle to surgery of the heart.[21, 31, 35] Recently Dodrill[8] successfully used it clinically, but in our experience,[4, 5] it appeared unwise to rely on substitution for one side of the heart only during operation because of the ever-present hazard of ventricular fibrillation. The amount of dissection and cannulation necessary

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made the simultaneous use of a pump for both sides of the heart seem impractical for clinical use. Therefore, one is left with the alternative of constructing a pump and oxygenator to maintain circulation while the heart and lungs are functioning. There have been three successful experimental approaches to this problem. Mustard and Chute[28] have suggested the use of a donor lung. The second is oxygenation of blood by producing a thin film to permit gas diffusion. This has been extensively studied by Gibbon and his associates,[11, 26, 27] Dennis and his group,[7] Dubbleman,[9] Björk,[2] Jongbloed,[19] and others.[25] A third technique, the use of bubbling oxygen through blood, was made practical by the introduction of polymethylsiloxane for the control of foaming by Clark, Gollan, and Gupta.[3] Subsequently this "dispersion" technique has been extensively studied by Helmsworth, Clark, and their associates[15, 16] and by Kolff and Olmsted.[22] Gimbel[12] described a method for using easily broken large blood bubbles to permit gas diffusion, which in concept is very like the first apparatus described in this paper. Because this idea seemed to offer possibilities, further development led to the Type II "large bubble" oxygenator, which was used in the majority of the experiments.

METHODS AND MATERIALS

The experiments to be reported were performed on mongrel dogs of 8 to 22 kilograms in weight. These were used as delivered to the animal farm without prolonged preoperative dietary or other preparation.

Arterial blood pressure was measured in every experiment with a mercury manometer. When tracings were made of arterial, venous, right auricular, or right ventricular pressures, they were made with a Grass oscillograph through Statham strain gauges. Simultaneous electrocardiograms and electroencephalograms were taken on the same apparatus. One lead for the electrocardiogram was placed in the right shoulder and the other precordially. Brain waves were taken from bipolar leads, one at the vertex the other at the occiput.

Blood flow was measured with a differential manometer connected to an orifice flowmeter in the venous line to the apparatus similar to that described by Green.[14] The orifice was of adequate size (1.2 cm.) not to obstruct the flow of blood. Subsequently, a rotameter[33] was used for this purpose. At times, pump action and speed were relied upon as indications of flow, being calibrated at the end of each experiment.

Blood oxygen and carbon doixide contents were measured by the method of Van Slyke and Neill.[37] Blood pH was determined with the Cambridge glass electrode. From these values, the blood carbon dioxide tension was estimated with the nomogram of Singer and Hastings.[34] Free hemoglobin was measured by determining iron content using a modification of the method described by Ponder.[30] Clotting times were determined by the Lee-White technique.[40] Sodium and potassium were measured with the Baird Associates flame photometer. Cultures were taken in beef broth, and grown for identification in the bacteriology laboratory.

PROCEDURE

When the Type I oxygenator and air-driven blood pump had been developed and had given good results with partial perfusion experiments, seventy-four "total perfusions" were undertaken in which no blood was allowed to pass through the heart and lungs while the apparatus was in operation. After heparinization, using 6 to 8 mg. per kilogram, plastic catheters* were placed in the superior and inferior venae cavae through a jugular and a femoral vein. A small catheter was introduced through the azygos vein into the right auricle and through the tricuspid valve to allow the tip to lie within the right ventricle for the removal of coronary venous blood. Defunction of the heart and lungs was accomplished by clamping the venae cavae. Nineteen total perfusions were per-

*Supplied by Clay Adams Co., New York.

formed in which the left pleural space was entered to permit dissection and clamping of the pulmonary artery during the experiment. In these two series the total perfusion was maintained for a minimum of twenty-five minutes and in the majority for thirty minutes or more, the longest being sixty-two minutes.

Included in the group of experiments on total by-pass of the heart and lungs are two series of operative procedures performed while the heart and lungs were temporarily prevented from performing their normal functions. Right ventriculotomy was performed fifteen times. The aorta was opened eighteen times. By the time the suture lines were completed, the venae cavae had been clamped for twenty-five to thirty minutes. Despite the additional factors, these experiments are included in consideration of total by-pass of the heart and lungs in that this was one of the severer tests to which the technique was put.

At the end of each perfusion, when the venous connections had been clamped, each animal was given, intra-arterially, sufficient blood from the apparatus to return, if possible, its arterial blood pressure to the preperfusion level.

All experiments were performed under pentobarbital anesthesia, 30 mg. per kilogram. This was supplemented by small doses as necessary during the procedure.

In the total by-pass experiments, control of postoperative bleeding was important. It soon became apparent that meticulous hemostasis during thoracotomy was essential, whether or not electrocautery was used. After the perfusion was completed, protamine in isotonic saline solution was administered slowly by intravenous drip. The standard technique finally employed consisted of giving the animal 1 mg. for each estimated milligram of heparin in the blood volume. If the clotting time was found to be over ten minutes, further protamine was given slowly until subsequent determinations indicated that the clotting time was less than ten minutes.

Oxygen, carbon dioxide, and acidity were measured in mixed venous blood entering the oxygenator and in samples obtained from an arterial cannula.

Blood cell destruction was estimated by comparing the amount of free plasma hemoglobin, cell counts, smear differential, and hematocrit determinations before and after perfusion. A layer of fine foam forming on the surface of the blood in the bubble trap suggested the presence of very small, almost microscopic, bubbles in the blood. Fine bubbles otherwise undetectable occasionally could be discovered with the aid of a slit lamp.

During the preliminary perfusion experiments, no attempt at asepsis was made. The apparatus was carefully cleaned with a detergent and rinsed with isotonic saline solution before use. However, all animals were permitted to recover, if possible, from the operation and only sacrificed if sepsis became evident later. Each animal was given either one dose of Bicillin 600,000 units* or 600,000 units of procaine penicillin intramuscularly daily for one week postoperatively. Using Type I and Type II oxygenators which were constructed of glass, permitting steam sterilization, twenty-eight experiments were conducted with as complete aseptic precautions as possible. Blood cultures were made from the apparatus at the termination of twenty-two of these perfusions.

Regardless of sepsis which might develop later, an animal was considered a "survivor" if it was apparently in good condition twenty-four hours later. This included the ability to walk, drink, respond to commands or attention, to see, and to urinate.

At the time of sacrifice, or as soon as practical after death, an autopsy was performed on every perfused animal. In addition to the gross examination of the abdomen and thorax, the brain was exposed to demonstrate the presence or absence of cerebral edema by the appearance of the gyri. Microscopic sections were taken from the brain, heart, lungs, kidney, and spleen of thirty-two animals.

OXYGENATORS

Experiments conducted with a variety of bubble blood oxygenators led to the development of two types dependent upon reflux columns in which large bubbles (2 to 8 mm.) are produced. Compared with the fine bubbles of the oxygen dispersion apparatus, the large

*Kindly supplied by Wyeth Incorporated, Philadelphia.

bubbles were easily broken, thus reducing the hazard of pumping foam into the arterial tree and eliminating extensive exposure of blood to antifoam substances. They are built of glass and easily disassembled for cleaning and autoclaving. The inner surfaces are coated with silicone.

Type I Oxygenator.—Illustrated in Fig. 1, it has a column 90 cm. high and 4.5 cm. in diameter. Through three jets at the top of this, venous blood is drawn by a slight negative pressure (–1 to –3 cm. Hg). The descending blood meets rising oxygen bubbles, over which it is spread for exchange of carbon dioxide and oxygen. As the bubbles approach the top of the column, they are in greater part broken by the rush of blood from the jets. Such bubbles or foam as rises above the jets is dissipated upon contact with marbles* coated with polymethylsiloxane (DC Antifoam A). From the bottom, blood passes into *Reservoir A* and then passes through an *auricle*, which is similar to that described by Dubbleman.[9] It is constructed of an inner flexible thin-rubber Gooch tube and an outer solid-glass casing. If the level in *Reservoir A* falls too low, the inner tube collapses and prevents the pump from drawing gas into itself. When the level is well up in *Reservoir A*, it serves as a ready source to fill the pump promptly during its suction phase.

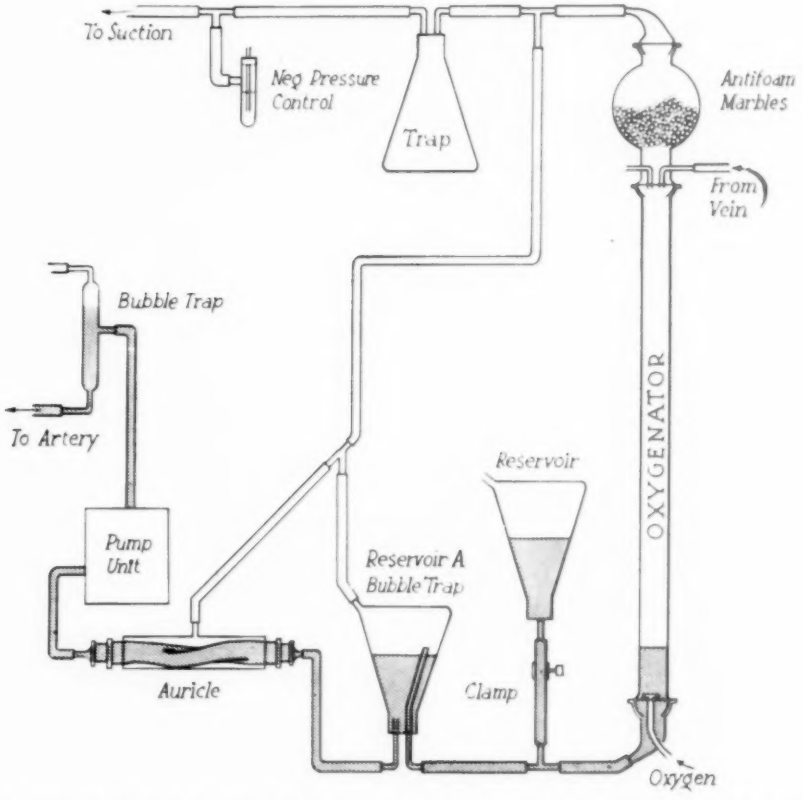

Fig. 1.—Diagram of Type I "large bubble" oxygenator, used in 58 per cent of the experimental total perfusions.

Type II Oxygenator.—The second form of apparatus, illustrated in Fig. 2, was evolved from the first to obviate the latter's tendency to allow small bubbles to flow into *Reservoir A*. Blood from the venous system enters the bottom of the oxygenating column under a negative pressure of 1 to 3 cm. Hg. There it is converted to bubbles (2 to 7 mm. diameter) by oxygen flowing through the bubbler at 5 L. per minute. As the bubbles rise and expand, many explode in the bubble-breaking chamber. The remainder progress until

*Manufactured by Dow Corning Corp., Midland, Michigan.

they encounter an air jet, which breaks the majority of them. Any that rise beyond this point are drawn into the chamber containing the antifoam-coated marbles, where the blood, freed of bubbles, falls back. Blood flows down the lower side of the bubble-breaking column to collect in a reservoir at its lower end. To be certain that the blood level in the reservoir will not drop to dangerously low levels, an *auricle* similar to that used in Type I is interposed in the connection to the pump.

Data on flow and oxygenating capacity of the two types of large bubble oxygenators are given in Table I. From this it may be seen that they are quite capable of adequately oxygenating and eliminating carbon dioxide from venous blood at flow rates listed in the fourth column.

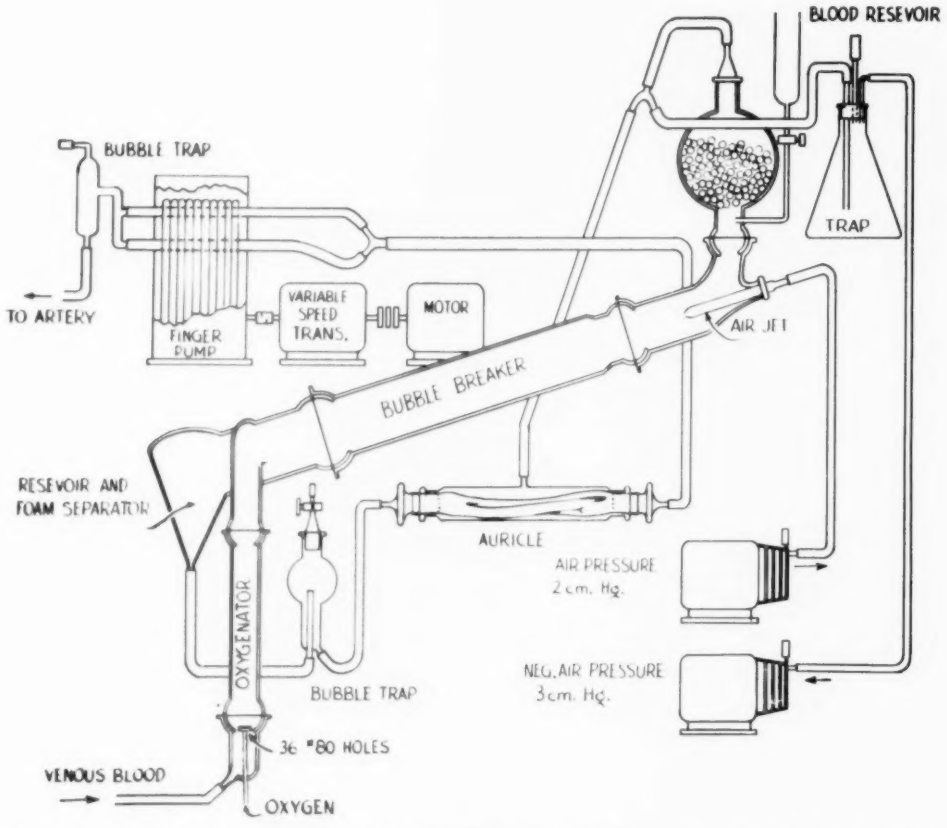

Fig. 2.—Diagram of Type II "large bubble" oxygenator, used in 42 per cent of the experimental total perfusions.

Blood Pumps.—Three types of pump were employed and tested: (1) a modified Dale-Schuster pump, (2) a finger pump,* and (3) a pump dependent upon air pressure as the driving force, similar in certain respects to that described by Sewell and Glenn[32] and employing one of the principles of the pump constructed by MacNeill.[24]

During the preliminary experiments it was observed that fibrin was often formed on the ball valves of the Dale-Schuster pump. The same was found to be true of flap valves and those made of thin flat tubing, as used by Dubbleman[9] and Kolff.[22] For this reason a system was desired in which there were no moving valve parts within the blood stream. Such a device was developed and is illustrated in Fig. 3. Blood is propelled by alternating positive and negative pressure outside a flexible gum-rubber tube. By placing the tube in a vertical position and allowing the blood to progress downward, the first portion to

*Manufactured by Sigmamotor Co., Watertown, New York.

TABLE I. FLOW AND OXYGENATING CAPACITY OF TYPE I AND TYPE II BUBBLE OXYGENATORS

OXYGENATOR	VOLUME TRAPPED INCLUDING PUMP	TOTAL FLOW CAPACITY (C.C. PER MIN.)	OXYGENATION AND CO_2 ELIMINATION				
			NO. OF DETERMINATIONS	FLOW RATE (C.C. PER MIN.)	AVERAGE OXYGEN INCREASE (VOL. %)	AVERAGE pCO_2 DECREASE (MM. HG.)	AVERAGE CO_2 DECREASE (VOL. %)
Type I small	1,050	1,200	18	1,200 (1,095-1,300)	9.8	14.3	19.2
Type I large	2,300	3,800	4	2,998 (2,800-3,100)	9.6	13.6	18.6
Type II small	1,300	1,600	15	1,154 (975-1,320)	9.8	14.2	22.1
Type II large	2,600	4,500	2	3,175 (3,050-3,300)	10.6	17.8	27.3

collapse as air pressure is applied around it is the upper end. This helps to prevent regurgitation. At either end, instead of mechanical valves, are placed short pieces of flexible tubing with outer glass casings about them. Air pressure of 15 pounds applied to these will cause the flexible tubes to collapse and will prevent regurgitation of blood under pressures up to 200 mm. Hg. Thus, by synchronously applying alternate positive and negative pressure, they can be made to act as valves for the central large propulsive

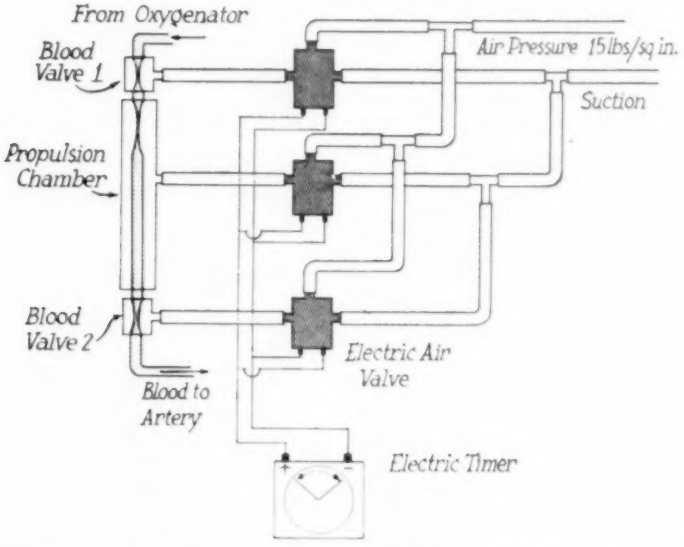

Fig. 3.—Diagram of the air-driven blood pump, used in the majority of the experimental perfusions. Blood enters at the top through *Blood Valve 1* when it and the tube in the *Propulsion Chamber* are under negative pressure. It leaves through *Blood Valve 2* during the pressure phase of the *Propulsion Chamber*.

tube. The air pressure and suction are controlled by three-way electric air valves,* which are energized through a timer† and made to alternate each second. A serious disadvantage became apparent when one of the valve rubber tubes perforated and the whole arterial system was filled with air. The volume output of the pump is controlled by adjusting the needle valve which controls the amount of air allowed to enter the central chamber.

Using aliquots of cross-matched outdated human blood, it was found that in one-half hour of recirculation through a cannula and reservoir, the air pump increased free

*Manufactured by Skinner Electric Valve Division, Skinner Chuck Co., Norwalk, Connecticut.

†Manufactured by Eagle Signal Corp., Moline, Illinois.

hemoglobin 64 mg. per cent, the finger pump 134 mg. per cent, and the oxygenator 442 mg. per cent. Similar results were obtained with ox blood. Because of its great variability in mechanical fragility, dog blood could not be used for this experiment.

RESULTS

Seventy-four experimental operations were performed in which the heart and lungs were temporarily excluded from the circulations for twenty-five minutes or more.

TABLE II. RESULTS OF TOTAL PERFUSIONS TWENTY-FIVE TO SIXTY-TWO MINUTES

	NUMBER OF EXPERIMENTS	SURVIVORS	MORTALITY (PER CENT)
Clamp venae cavae or clamp pulmonary artery	41	17	59
Clamp venae cavae plus right ventriculotomy			
Series I	5	2	60
Series II	10	10	0
Clamp pulmonary artery plus open aortia			
Series I	8	2	75
Series II	10	9	10
Total	74	40	46

The over-all mortality was 46 per cent. The majority of these deaths occurred early in this experimental series. Toward the latter part of it, it was possible to perform twenty consecutive operations, each involving cardiotomy or incision into the aorta with a mortality of 5 per cent. First, data on the apparent causes of death, given in Table III, will be presented, followed by the results of physical and chemical observations on the group as a whole.

TABLE III. CAUSE OF DEATH IN TOTAL PERFUSION

Mechanical failure of apparatus	2
Clot formation in apparatus	2
Fibrin formation and emboli	4
Gas emboli	3
Postoperative hemorrhage	14
Unexplained (low blood pressure)	9
Total	34

These figures do not include sixteen deaths from empyema which occurred three to twenty-one days postoperatively.

Emboli.—Examination of the blood in the tube from the pump to the arterial cannula revealed that in at least one-half the perfusions made with the small Type I oxygenator, a few very small bubbles were pumped into the arteries. Four times a layer of foam over one-fourth inch in thickness was found in the bubble trap at the end of the procedure. Three of these animals died postoperatively within the first twenty-four hours. At autopsy, brain edema was demonstrated in two.

Fibrin deposited in small strings on the glass walls of the apparatus wherever foam collected in a static state. This was particularly prone to occur in the reservoir. Little emboli presumably broke away and were carried away into the arteries. Four animals which apparently underwent satisfactory perfusions in other respects died in coma. Fibrin was actually demonstrated in the tubing at the termination of all four procedures. At autopsy all showed microscopic infarcts in the kidney parenchyma. These were septic in one animal that survived in coma for fifty-six hours. Another showed small areas of focal necrosis in the spleen. Brain edema was thought to be present in two,

but in only one of these was microscopic evidence of infarction demonstrated. During the use of both Type I and Type II oxygenators, thick fresh blood films examined under the microscope revealed a tendency toward red-cell clumping. This was seen to a considerably lesser extent in preoperative films.

Clotting Mechanism.—Postoperative hemorrhage was the apparent cause of fourteen deaths, the greatest from any one cause. Death following six of the operations in the first series of cardiotomy and aortic operations was due to hemorrhage from the pericardium, suture lines, and other points within the chest. Meticulous hemostasis and the use of protamine controlled by serial clotting-time determinations proved quite adequate in the majority of animals. But following the evolution of this technique, there were four animals in which adequate clotting could not be made to occur. In all but one of these there had been a consistently low mean arterial blood pressure throughout the perfusion (45 to 65 mm. Hg). Blood cultures were obtained from three of these animals which had been perfused aseptically. One grew out predominantly *Escherichia coli*, the second *Bacillus pyocyaneus*, and the third *Bacillus proteus*. The incidence of postoperative fatal hemorrhage was not greatly different in those animals which had been perfused aseptically and those which had not, being 15 per cent in the former and 21 per cent in the latter.

On three occasions the amount of heparin given the perfused dogs and donors was reduced below 6 mg. per kilogram of body weight; clotting followed by death of the animal occurred twice.

Blood Pressure.—If the experiments in which an obvious cause of death was apparent be eliminated the arterial blood pressure records during perfusion fall into three categories: *Group I survivors:* None of these eighteen animals during the procedure had a mean arterial blood pressure of less than 85 at any time. The average of their pressures remained about 100 mm. Hg throughout the procedure. All recovered rapidly. *Group II survivors* including twenty-two total perfusions exhibited a rather profound fall of mean arterial blood pressure within two or three minutes after the circulation through the heart and lungs was stopped. The average level at the end of ten minutes was 69 mm. Hg. Thereafter, it rose gradually to 78 mm. Hg at the end of the perfusion. Three fell below the level of 60 mm. Hg but none for a period longer than ten minutes. Only one reached the level of 85 mm. Hg within the first ten minutes. The arterial blood pressure data of *Group III*, labeled "Unexplained Deaths," are given in Fig. 4. These nine records are reproduced in full to show that all but one animal had a blood pressure below 50 mm. Hg for a period of not less than fifteen minutes. Two had blood pressures below 40 mm. Hg for periods of only ten minutes. In no animal of this group was there an amount of blood in the chest considered sufficient alone to have been responsible for death.

Hemodynamics and Blood Flow.—There was a wide spread in the mean pump outputs of the perfusions, ranging from 112 c.c. per kilogram of body weight in a survivor down to 42 in one of the death group. The highest average flow recorded among the animals which died was 84 c.c. per kilogram per minute; the lowest in any survivor was 55 c.c. per kilogram per minute. No correlation can be made between blood flow through the pump and arterial blood pressure level for the whole group of experiments.

The volume of blood which it was found possible to pump practically through a cannula with a 3 mm. bore is approximately 650 c.c. per minute. Above this, hemolysis becomes excessive and pressures within the pump rise above 300 mm. Hg. On the other hand, up to 1,800 c.c. per minute was pumped through a cannula of 5 mm. diameter. Through a cannula of 8 mm. diameter was pumped 3,400 c.c., without difficulty.

Venous drainage is equally a limiting factor to pump output, for only as much blood can be returned to the animal as enters the oxygenator. To illustrate this matter, the flow and pressure record of a perfusion are given in Fig. 5. In this typical experiment, when one of the venous catheters temporarily was clamped, the arterial blood pressure, which had been near 90 mm. Hg, fell within two minutes to 66 mm. Hg. A similar situation, illustrated in Fig. 6, occurred if blood was allowed to collect within the veins because of inadequate suction upon the venous catheters.

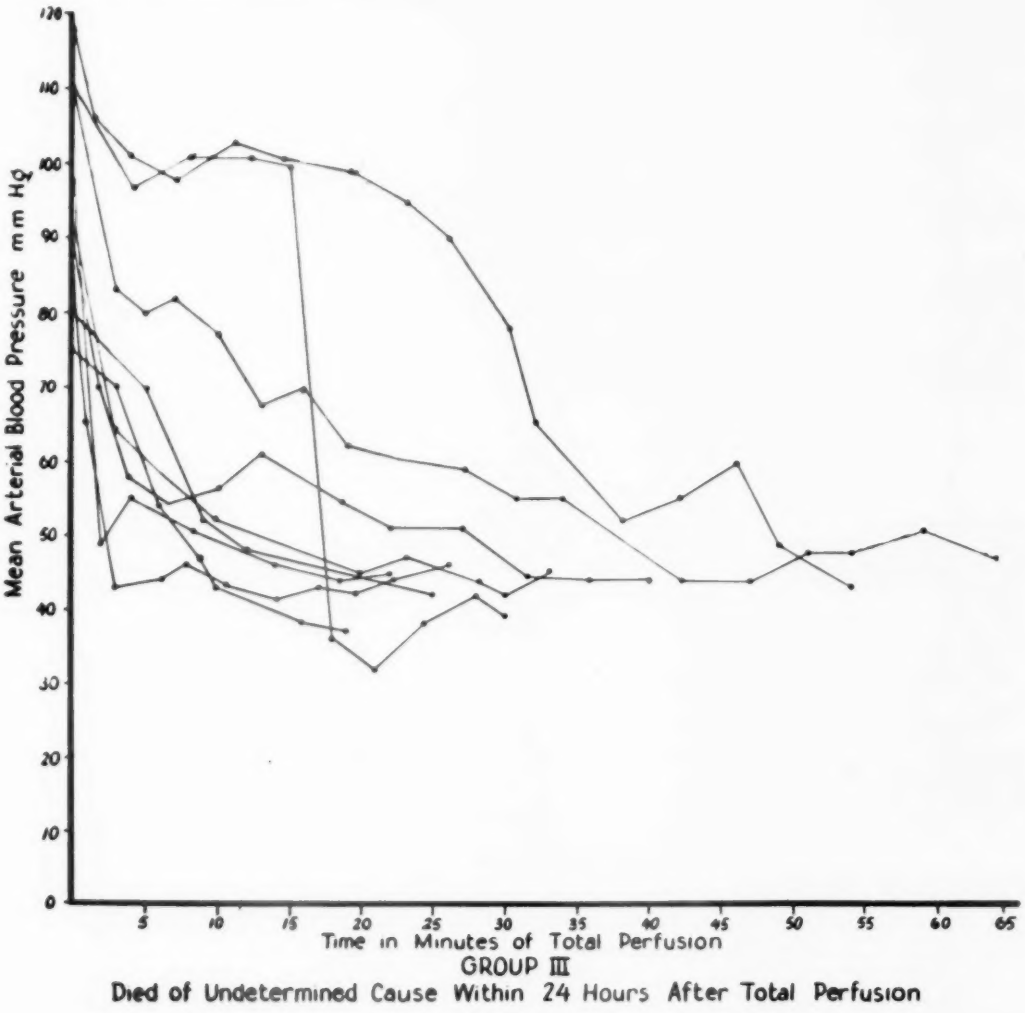

Fig. 4.—Blood pressure record during the total perfusion of Group III animals.

The response to hemorrhage varied among the dogs. In six, quantities of blood estimated up to 500 c.c. were lost from the circuit with only a moderate fall in pressure. The addition of blood resulted in prompt return of pressure to 90 mm. Hg or above. All of these recovered. Three dogs in Group III, following a similar blood loss, failed to respond with more than a transient rise.

The prompt fall in blood pressure at the start of total perfusion in Group II was followed in 76 per cent of the animals by a gradual rise of pressure to 75 mm. Hg or above without the addition of any extra blood. On the other hand, in 18 per cent of Group II and 67 per cent of Group III there was a

gradual fall of blood within the reservoir despite the apparent absence of hemorrhage. Simultaneously, there was a continuous fall of blood pressure. Whereas the majority of the Group II animals responded to transfusion at the end of the procedure by a sustained rise of blood pressure, only two of Group III did so.

Temperature.—The average temperature drop during perfusion was 3.2° C. This ranged from 2.2° to 6.1° C.

Electroencephalogram.—In the course of forty-two total perfusions, electroencephalographic tracings using a vertex-occipital lead were made at frequent intervals. The pattern from the Group I survivors in every case showed but little change in either potential or frequency from the preperfusion tracing. Postoperatively these animals recovered rapidly, often being conscious and standing within three hours. An example of such a set of tracings is given in Fig. 6.

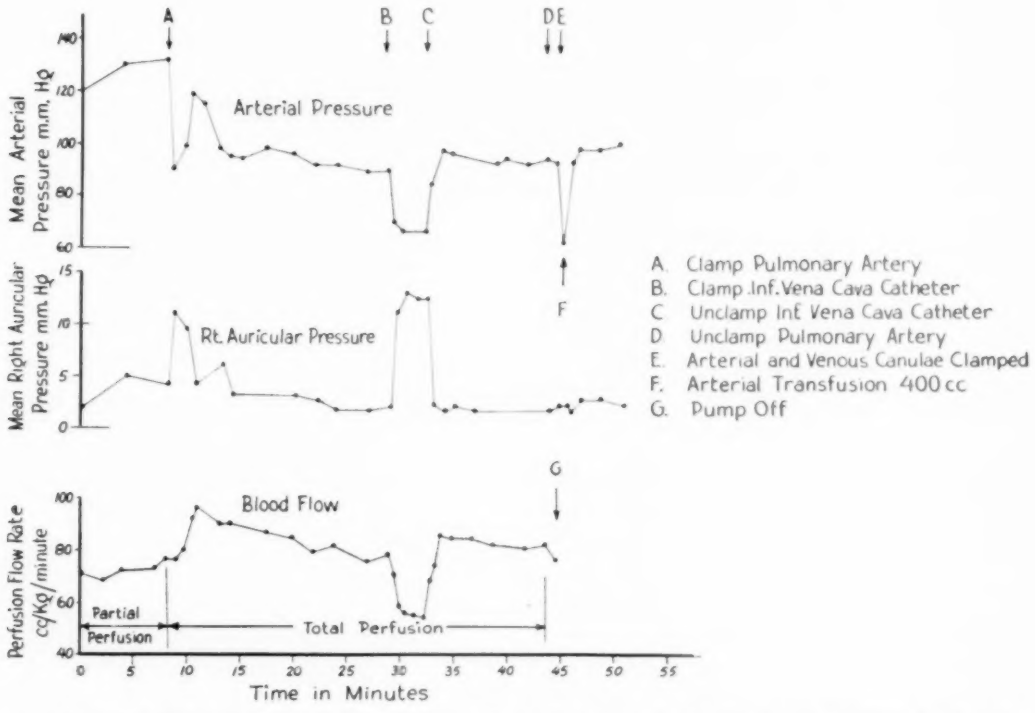

Fig. 5.—The record of a total perfusion of a Group I animal which survived, to show the effect of temporarily impaired venous drainage on arterial blood pressure, right auricular pressure, and pump output.

The patterns obtained in the Group II survivors, those in which the blood pressures fell to levels between 60 and 80 mm. Hg, showed moderate depression of frequency in all and a decrease of voltage in seven of the thirteen.

In the tracings from the Group III animals which subsequently died, the potential was reduced to almost zero at one time or another. The least time that such a "flat" pattern was recorded was ten minutes. In contrast to the survivors, these animals did not exhibit, during the immediate postoperative period, the typical brain wave patterns of the lighter stages of barbiturate anesthesia.[10] Instead, those Group III animals remained in coma, and such brain waves as did reappear were of low potential and low frequency, as demonstrated in Fig. 7, two hours after the perfusion. Three of these five

animals, all of which died within fifteen hours, exhibited some gross evidence of brain edema at autopsy. Microscopic evidence of cerebral infarction was demonstrated in one.

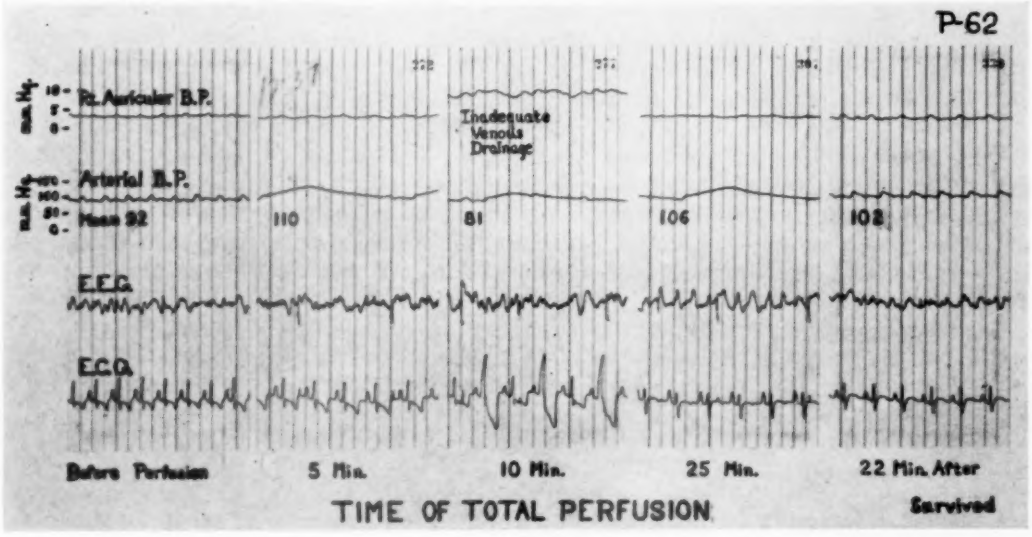

Fig. 6.—Reproductions of the oscillographic recordings during the total perfusion of a Group I animal to show normal electroencephalographic tracing and blood pressure.

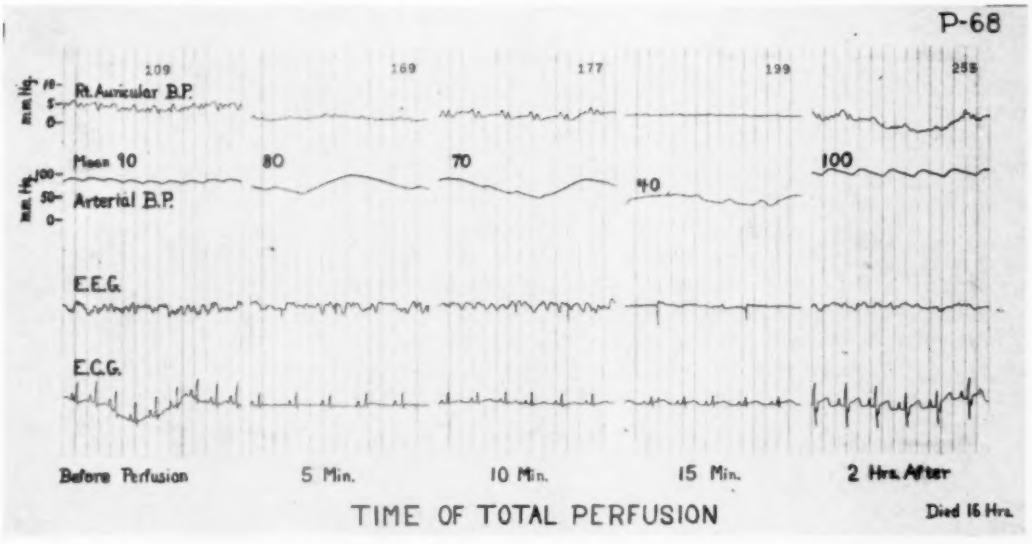

Fig. 7.—Reproductions of the oscillographic recordings during the total perfusion of a Group III animal which died, to show depression of brain wave potential and fall of blood pressure.

An electroencephalogram taken on one of the animals which died of gas emboli showed the brain waves to be of progressively less potential. At the point when the total perfusion had been in progress for twenty-five minutes, there was a flat tracing with no potential. Thereafter, no indication of returning brain wave activity was seen. The animal died ninety minutes after the operation was terminated.

Electrocardiogram.—When the work of pumping blood was removed from the heart, as with a clamp-off of the venae cavae, the heart rate decreased. On the other hand, if a rise in pressure occurred in the right ventricle and right auricle when the pulmonary artery was clamped, the heart rate increased (Bainbridge reflex), and if the strain became excessive (above 10 mm. Hg right auricular pressure), a depression of the S-T segment occurred. Not infrequently this was accompanied by ventricular extrasystoles as seen in the central tracing of Fig. 6. Inversion of the T waves with depression of the S-T segment was seen also in animals of Groups II and III during periods of hypotension below 60 mm. Hg.

Blood Gas and pH.—The acceptable data from the animals which underwent total perfusion are summarized in Table IV. These include determination of oxygen percentage saturation, carbon dioxide tension, and pH in blood obtained immediately before perfusion and shortly before the termination of total perfusion. Arterial values were obtained in twenty-six animals, but in only twenty are these data available for venous blood. They have been placed in three categories according to which of the blood pressure groups the animals were in. Since the number of determinations from animals in Group III, "Unexplained Deaths," is small, they are not of value statistically but are simply included for comparison.

TABLE IV. ARTERIAL AND VENOUS BLOOD GAS AND pH IN TOTAL PERFUSIONS

	ARTERIAL			VENOUS		
	% O_2 SATURATION	pCO_2 (MM. Hg)	pH	% O_2 SATURATION	pCO_2 (MM. Hg)	pH
Group I Survivors						
Preperfusion						
Mean	*95.3*	*27.6*	*7.36*	*73.2*	*37.0*	*7.30*
Standard deviation	0.26	9.58	0.08	5.13	3.63	0.06
No. of determinations	10	10	10	9	9	9
End total perfusion						
Mean	*84*	*31.9*	*7.28*	*59.4*	*46.6*	*7.20*
Standard deviation	13.3	4.4	0.07	7.2	7.4	0.06
No. of determinations	10	10	10	9	9	9
Group II Survivors						
Preperfusion						
Mean	*89*	*31.2*	*7.33*	*67*	*43*	*7.25*
Standard deviation	7.3	7.2	0.09	14.7	14.6	0.09
No. of determinations	12	12	12	8	8	8
End total perfusion						
Mean	*89*	*36.6*	*7.19*	*47.5*	*63*	*6.98*
Standard deviation	7.55	12.9	0.14	7.78	9.76	0.09
No. of determinations	12	12	12	8	8	8
Group III Deaths (low blood pressure)						
Preperfusion						
Mean	*92*	*29*	*7.34*	*70*	*43*	*7.25*
Range	90-93	26-33	7.28-7.44	64-74	37-50	7.23-7.28
No. of determinations	4	4	4	3	3	3
End total perfusion						
Mean	*93*	*38.3*	*7.06*	*29*	*93*	*6.92*
Range	88-98	24-55	7.04-7.08	20-36	3	6.90-6.95
No. of determinations	4	4	4	3	3	78-106

It will be noted that in the arterial bloods obtained before perfusion from the three groups, there is little difference. The same is true of the arterial bloods obtained at the end of the total perfusion, with the exception of pH

values, which are progressively higher in Groups II and III. It is of importance that the mixed venous blood contained less oxygen in each group after the perfusion. The venous pCO_2 was similarly higher and the pH lower at the end of the clamp-off period in Group II, and even more so in Group III.

Electrolytes, Protein, and Hemoglobin.—Potassium determined in eight experiments showed little over-all change from the preferfusion level to that at the end of the procedure. There was one exception, an animal in Group III in which the plasma potassium rose from 3.26 to 5.28 meq. per liter. Sodium and chloride showed no significant changes. The blood total protein rose in six animals from an average of 6.2 to 7.9 Gm. per cent, and fell slightly in eight to 5.8 Gm. per cent at the end of perfusion. Examination of the plasma from three dogs in the electrophoresis apparatus revealed little change in the blood protein constituents as a result of the perfusion.* Only the hemoglobin was increased. Free plasma hemoglobin increase at the end of perfusion varied greatly among the animals, ranging from 121 to 398 mg. per cent. The incidence of high values occurred almost equally in all three groups.

Bacteriology.—Of the twenty-eight perfusions made with complete aseptic precautions, including steam sterilization of the apparatus, satisfactory cultures were obtained from the blood in the apparatus at the termination of twenty-two. Six showed no growth. The remainder showed a variety of organisms including *Staphylococcus aureus, Staph. albus, B. pyocyaneus, B. proteus, B. coli,* and *Aerobacter aerogenes.* There were seven cultures in which *B. coli* or *coloform bacilli* were found, one in Group III, two from animals which died of hemorrhage, and four from survivors in Group II.

Among the animals not perfused sterilely, hypopyon developed in the eyes of seven animals two to five days postoperatively. Cultures were made from two of these eyeballs at the time of autopsy. In neither did any growth occur. Some degree of wound infection developed in the great majority of the animals, and sixteen died of empyema.

Autopsy Findings.—Six animals, in good condition, were permitted to survive periods ranging from six to eleven months before being sacrificed. Gross examination revealed old healed infarcts of the kidneys in one. Except for pleural and pericardial adhesions and the well-healed aortic incision in one and myocardial scars in two, no abnormalities were found. Microscopic sections failed to reveal other abnormalities in any of the organs examined.

Of the thirty-four animals which died of infection or were sacrificed between five days and three weeks, the majority of the lesions were related to the septic process. Interstitial myocarditis was seen microscopically in one. The brains of this entire group were normal in appearance and microscopically, but kidney infarcts were found in three and splenic infarcts in two.

Among the animals which died in the immediate postoperative period, brain edema was considered to be present grossly in 60 per cent. Microscopic sections revealed cerebral infarcts in four. Various lesions caused by sepsis were observed.

CLINICAL EXPERIENCE

CASE 1.—B. McG., U 6810, a 5 pound, 4 ounce premature white male infant, was observed to be cyanotic shortly after a normal delivery. Physical examination was otherwise normal, breath sounds and heart sounds not being unusual. The patient was placed in an oxygen incubator but continued to become more cyanotic during the next few hours. Twelve hours later he appeared to be in extremis, and despite the lack of a definite diagnosis, it was believed that exploration was justified with the possibility of finding an anomaly of the great vessels which might be corrected with the aid of the oxygenator and pump.

*Through the kindness of Dr. Lena Lewis, Cleveland Clinic, Cleveland.

When brought to the operating room in the incubator thirteen hours after birth, there was extreme cyanosis. The limbs were flaccid and respiration was labored. When the patient was placed on the operating table, respirations were assisted by the anesthetist using 100 per cent oxygen.

The sterilized small Type I oxygenator was filled with 1,000 c.c. of blood cross-matched with the patient's blood. Before use, to each 500 c.c. unit of citrated blood was added 50 mg. of heparin followed by 10 c.c. of 10 per cent calcium chloride solution. The patient was then given heparin 20 mg. intravenously. A small cannula was placed in one femoral artery and connected to a mercury manometer. Polyethylene catheters of 2 mm. inside diameter were then introduced into the axillary and both femoral veins. These were connected to the input jets at the top of the oxygenator. A blunted No. 18 needle was tied into the axillary artery as a cannula and connected to the output line of the pump.

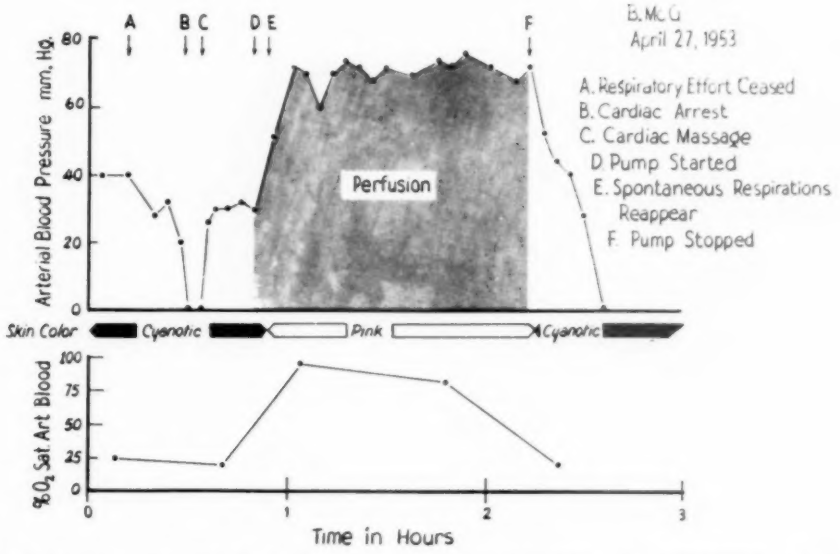

Fig. 8.—Graph of perfusion of Case 1, a 14-hour-old infant. Postoperative diagnosis was nonpneumatization of the lung.

Shortly after the patient's arrival in the operating room, respiration ceased, and soon cardiac arrest occurred. Massage of the heart was able to maintain a blood pressure of about 30 mm. Hg, although the infant remained cyanotic and made no effort to breath. The oxygenator and pump were started. Within four minutes the child's color changed from blue-gray to pink, and three minutes later spontaneous respiratory efforts started, which gradually became well-organized respiratory movements. The blood pressure gradually rose to 75 mm. Hg, remaining between 65 and 75 mm. Hg throughout the remainder of the perfusion, as illustrated in Fig. 8.

The heart itself, which had been flaccid, began to beat after fifteen minutes of perfusion and became progressively more forceful. Spontaneous movements of the extremities occurred, but the wink reflex did not reappear. No abnormality being found, the thoracotomy was closed. During this period the output of the pump was approximately 200 c.c. per minute. Because of mechanical difficulty it was necessary to shut off the apparatus after eighty-four minutes of perfusion. The patient rapidly became cyanotic again and was pronounced dead twenty minutes later.

Analysis of arterial blood samples for oxygen saturation showed only 25 per cent saturation preoperatively compared with 90 per cent after the perfusion was started. Blood culture at the end of the perfusion gave no growth. At autosy the diagnosis of nonpneumatization of the lung was made.

CASE 2.—G. P., U 1459, a 55-year-old white man, entered the hospital for the third time in severe cardiac failure.

Physical examination revealed a poorly nourished white man 62 kilograms in weight lying propped up in bed, somewhat dyspneic with extensive dependent edema, with a thrill and harsh systolic murmur at the aortic area. Diastolic and systolic murmurs were also heard at the apex. A cardiac catheterization on a previous admission showed marked elevation of both pulmonary arterial and "wedge pressures."

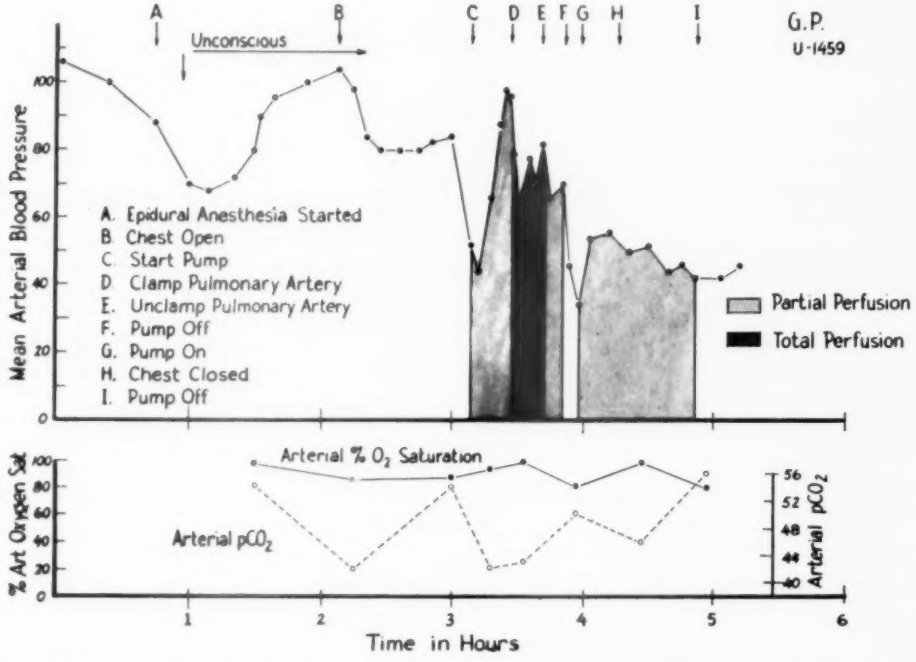

Fig. 9.—Graph of perfusion of Case 2, a 55-year-old man. Diagnosis was aortic and mitral stenosis and severe cardiac failure.

A diagnosis of aortic stenosis with moderate mitral stenosis and regurgitation was made. He progressed downhill despite therapy. On the twentieth hospital day the patient was taken to the operating room. An endotracheal tube was passed with topical anesthesia. Under extradural block of the upper thorax, hypotension developed but responded to the administration of a vasopressor drug. At this time the patient became comatose. An anterolateral incision into the right pleural space was made. The sternum was transected, giving excellent exposure for dissection of the aorta and pulmonary artery. Heparin, 400 mg. was administered intravenously. The large Type I oxygenator and air-driven pump were connected to venous and arterial cannulae. The blood pressure, which had started to fall before the partial perfusion, rose within fifteen minutes to 100 mm. Hg. After the pulmonary artery was clamped, the aortic valve was exposed. A cut was made in one fused commissure under direct vision. The serrated clamp was reapplied to the aortic incision after the vessel had been refilled with blood. Circulation to the coronary arteries had been interrupted for six minutes. The heart did not stop beating. It promptly returned to a good pink color and continued to beat forcefully. In all, total perfusion lasted fifteen minutes, during which time the arterial blood pressure remained between 70 and 80 mm. Hg. The electrocardiogram showed little change except for a depression of the S-T segment during the period when coronary arteries were not being perfused. The output of the pump during this period was estimated at 3,100 c.c. per minute. Nine minutes later it was stopped. Blood pressure fell, and arrest occurred followed by ventricular fibrillation.

The pump was started again with a return of blood pressure to 55 mm. Hg. Defibrillation was accomplished with electric shock. The pump was continued in operation for fifty-one minutes while the output was gradually decreased until the heart appeared able to continue maintenance of circulation; protamine was administered by intravenous drip. The chest was closed. Spontaneous respiration did not reappear, and the heart ceased beating one-half hour later. This record is shown in Fig. 9.

Analysis of arterial blood samples revealed that oxygen saturation and pCO_2 remained within normal limits during the period of perfusion. The potassium rose from 3.9 to 4.8 meq. per liter. Calcium rose from 11 to 13.6 mg. per cent. There was considerable hemolysis present, but no exact value was obtained. There was no growth in a culture obtained at the termination of perfusion.

Autopsy revealed rheumatic involvement and stenosis of the aortic, mitral, and tricuspid valves. In addition to the 0.5 cm. incision in the posterior commissure, there was a 0.4 cm. stab wound in the medial cusp, which had perforated the ring. An old infarct was found in the brain, but no edema or fresh vascular lesion. In addition to a large organizing thrombus in the right pulmonary artery, there was congestion and edema of the lung and other organs.

CASE 3.—P. McG., U 6942, a 44-year-old white housewife, was admitted for the second time because of intermittent, very severe pulmonary edema and loss of consciousness. Six months previously exploration of the left auricle revealed a normal mitral valve with a large friable tumor to be present in the auricle measuring approximately 7 cm. in diameter. It was deemed impossible to remove it at that time without serious danger of fatal embolism or hemorrhage. After discharge she was admitted twice to an outside hospital in serious pulmonary edema. On the last occasion she almost died.

On admission, examination revealed a well-developed, somewhat thin woman 55 kilograms in weight with a well-healed left thoracotomy incision. Râles were heard at both lung bases. The heart was enlarged and the rhythm was regular with a soft diastolic murmur at the apex. Laboratory examination of blood and urine was normal except for a corrected sedimentation rate of 40 mm. per hour.

On the fourth day the patient was taken to the operating room. Under Pentothal and ether endotracheal anesthesia the femoral vessels were dissected, and a manometer was connected to the left radial artery. She was then placed in the lateral position, and the left pleura was entered through the old incision. With some difficulty the left auricle and pulmonary artery were dissected free of surrounding stuctures. As may be seen in Fig. 10, in which is reproduced a portion of the operative record of this patient, a fall of blood pressure occurred shortly after the pleura was entered, although blood had been carefully replaced intravenously from the onset of the procedure. The hypotension was shortly preceded by a marked peripheral vascular change in that the skin became cold and the fingernails gray. However, heart action, pulse, and electrocardiographic tracing remained unchanged. Blood pressure responded to 0.1 c.c. of neosynephrin intravenously. The peripheral vascular picture did not change throughout the remainder of the operation. Catheters were introduced into each femoral vein so that one tip lay near the right auricle and the other in the lower portion of the inferior vena cava. Into the right superficial femoral artery was inserted a 7 mm. cannula. These were connected to the large Type II oxygenator and finger pump, which were filled with 2,500 c.c. of citrated blood with added heparin, but no calcium. When partial perfusion was well under way, a clamp was placed on the pulmonary artery. The auricle was opened widely by a 10 cm. incision, and a dry field was maintained with the loss of only a little blood while the tumor was resected. Air embolism was avoided by placing a retractor through the mitral valve.[5] Because of difficulty in closing the scarred auricular wall, the total perfusion lasted twenty-two minutes. The pump, which averaged about 3,400 c.c. output per minute, was shut off seven minutes later. Excellent heart action continued.

The electrocardiogram revealed that normal heart action continued throughout the procedure except for ventricular extrasystoles when undue traction was put on the retractor in the heart. At the onset of total perfusion there was a transient depression of the S-T segment and a biphasic T wave. At the termination of the operation there was moderate prolongation of the QRS complex. This was largely corrected by the administration of 15 c.c. of 10 per cent calcium gluconate intravenously. Rectal temperature dropped from 98.8° F. to 96.0° F. during the procedure.

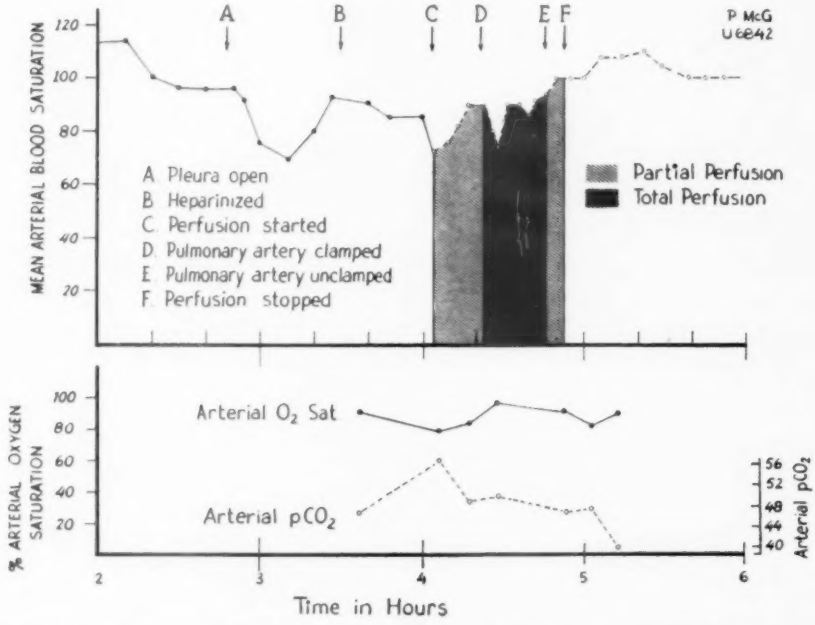

Fig. 10.—Graph of perfusion of Case 3, a 44-year-old woman. Diagnosis was large organized ball-valve thrombus of left auricle.

When the operation was completed a slight asymmetry of the pupils was noted, which shortly disappeared. Postoperatively she recovered quickly, but did not regain full consciousness. She thrashed about in bed and uttered little cries. Blood pressure remained between 90 and 100 mm. Hg systolic except for a transient fall to 70 mm. Hg three hours after the operation, when a further transfusion of 500 c.c. of blood was given. An electrocardiogram shortly after this was essentially normal. She remained aneuric. Six hours postoperatively the skin became cold, and the blood pressure rapidly fell. Respiration ceased, and she did not respond to artificial respiration or other resuscitative measures.

The arterial pH before perfusion was 7.23. This fell to 7.11 but rose at the end of perfusion to 7.25. Other blood chemical determinations were within normal limits except for free hemoglobin of 382 mg. per cent at the termination of perfusion.

At autopsy the brain showed evidence of old atrophy and no edema. A recently healed cerebral infarct was found with no evidence of acute vascular occlusion. There were 620 c.c. of blood and clots in the chest without evidence of cardiac tamponade. The suture line in the auricle was intact with a small mural thrombus attached to the mid-point. In the right lung was an old infarct, while on the left was a fairly recent one, which probably occurred in the preoperative period.

DISCUSSION

Only by experiments in which the heart and lungs are temporarily defunctioned does it appear possible to evaluate fully the ability of a pump and oxygenator as a means for artificially continuing the circulation. If the cardio-

pulmonary system is allowed to remain partially in operation, it makes up for the deficiencies of the apparatus in the maintenance of blood flow, blood pressure, and the respiratory exchange of gases. For this reason, it is important that thirty-four of the animals died following total perfusion in this series of seventy-four experiments. Excluding the fourteen which died of hemorrhage, it is probable that the remainder of the immediate postoperative deaths were directly attributable to the apparatus or the technique of its use.

The production of emboli, gaseous or particulate, is a serious matter in that cerebral damage followed almost all perfusions in which either was definitely observed. Fibrin strings were seen to form at points in the apparatus where foam rested for any length of time. Whether small particles broke off and entered the blood stream in the majority of the experiment is a matter hard to evaluate, for filters placed in the line tend to form fibrin themselves and, therefore, cannot be used.[4] Very small bubbles also are difficult to detect. Although they were seen at one time or another in one-half the perfusions with the Type I oxygenator and occasionally when Type II was in use, it is probable that they occurred more often. Kolff and Olmsted[22] have observed them in the use of a gas-dispersion oxygenator. However, they believe that dogs can stand the intra-arterial infusion of a considerable quantity of such fine bubbles, particularly if the blood is somewhat unsaturated. It is possible that this explains the fact that the animals which did well in Group I had somewhat lower arterial oxygen saturation than the others. Helmsworth[16] reported a similar finding. On the other hand, it is possible that with the somewhat greater flows in Group I as compared with Groups II and III, the apparatus was oxygenating the blood that passed through it to a slightly lesser extent. It has been suggested that the use of an ultrasonic flowmeter would promptly detect such fine bubbles.[20] Perhaps this should be applied to various types of oxygenators, especially those dependent upon bubbles or gas dispersion. It appears equally difficult to demonstrate brain damage from emboli or vascular occlusion by pathologic means. In only three of seven animals were cerebral infarcts found when known embolization had occurred.

That brain damage may well be the factor responsible for death in Group III, the animals which had blood pressures below 50 mm. Hg during perfusion, is strongly suggested by the electroencephalographic studies, which showed in five of these animals little or no potential at one time or another during the clamp-off of the heart and lungs. Gibbs, Gibbs, and Lennox[10] found that recovery of brain wave activity was proportional to the time that the brain waves were absent during anoxia, and that death occurred if this was prolonged to ten or twelve minutes. This finding was confirmed by Hopkins and Clowes[18] during profound depression in hypercapnia. Also it has been observed that brain wave activity is greatly depressed at low blood pressures. However, the depression in an intact dog is not great at blood pressures of 40 to 50 mm. Hg. It would then appear that other factors were responsible for this change.

The fall of blood pressure and failure to regain normal levels despite blood flows up to 85 c.c. per kilogram per minute in some of the Group III animals suggests a failure of the vasomotor system. So also does the observation of the gradual loss of blood from the reservoir as the blood pressure fell during the perfusion of six dogs in Group II and five in Group III. This took place despite adequate venous drainage of blood to the apparatus and apparent absence of abnormal blood loss. This is not the picture of oligemic shock manifested by several animals which recovered after low blood pressures related to inadequate pump output. It resembles more closely normovolemic shock, as described by Wiggers.[39]

The blood gas studies show that blood essentially normal in oxygen and carbon dioxide tension was being delivered to the animals from the apparatus throughout the perfusions, but the development of some degree of metabolic acidosis and the fall of oxygen in the returning venous blood suggest that the tissues were not being adequately perfused, especially in Groups II and III. Dennis and associates[7] have drawn attention to this phenomenon as a cause of hypotension and even death. The values for venous oxygen at the end of perfusion in Group I are slightly greater and those of Group II slightly less than the corresponding values given by Miller, Gibbon, and co-workers[27] for dogs which underwent perfusion for repair of experimentally produced septal defects. However, the considerable increase in pCO_2 in the venous blood during perfusion of the dogs in Group II and even more so in Group III suggests that aerobic metabolism was also continuing in the tissues. This is different from the results of Yandell Henderson,[17] which indicated that in oligemic shock the carbon dioxide content of venous blood was reduced to two-thirds or three-quarters of normal.

The work of Nelson[29] and its application to perfusion experiments by Dennis and his co-workers[7] implicated the presence of paracolon bacilli in the blood stream as a cause of fatal shock. It is certainly true that these organisms are found terminally in many conditions. But in the blood of only two of the several dogs that died in this series were they found. On the other hand, they were isolated from the blood of a number of animals in Group II which survived.

Intact dogs do not die ordinarily from hypotension of the degree and duration to which these animals were subjected.[18, 38] It seems likely that the cause of death in Group III was more akin to the vasomotor lack of response which precedes death in normovolemic shock. Since the blood chemical studies revealed no marked variation of electrolytes or proteins among the animals and since the degree of blood cell destruction was essentially the same in all three groups, it appears likely that the cause of tissue death was minute undetectable emboli, either gaseous or particulate. It is impossible to say which organs were affected, but it is likely from the electroencephalographic patterns that the brain was damaged early despite the inability to demonstrate the changes histologically. It is conceivable that increased viscosity or the tendency for

red cells to clump may have reduced perfusion of certain tissues. Fibrin or bubbles may have been the responsible agent. It is interesting that this did not occur in all animals, and the factors responsible remain for further investigation.

From Cases 1 and 2 it is impossible to draw any conclusions as to brain damage, for they had shown evidence of such injury before perfusion was undertaken, but in Case 3 there is little doubt that cerebral damage occurred. Postoperatively the patient in Case 3 resembled patients who die following unsuccessful cardiac resuscitation. Examination of the ocular fundi before death revealed no vascular abnormality. Careful examination of the brain at autopsy failed to reveal edema or recent infarct, nor in numerous sections examined was there any histologic evidence of microscopic occlusion of vessels large or small.

Despite the success in carrying out a series of experimental operations, which made it seem justifiable to undertake perfusion of hopelessly ill patients, the unsuccessful aspects of this experiment have been emphasized. This is done primarily to draw attention to a phase of the problem of artificial blood oxygenation which may have been overlooked, the probability of tissue damage as a cause of shock and the possibility of this injury resulting from undetected arterial emboli.

We are left, then, with the conclusions that to attain success in total perfusions the following criteria must be met:

1. The oxygenator must be capable of effectively eliminating carbon dioxide and adding oxygen to the blood which it pumps. This condition has been met in these experiments.

2. The venous drainage, the arterial cannula, and the pump and oxygenator output must be adequate to provide a flow of blood not greatly different from the normal cardiac output. This condition has been met only partially in these experiments. It appears that the maintenance of blood pressure is related only in part to pump output.

3. Blood cell destruction should not occur to any degree. This condition has not been met, but apparently did not have a marked bearing on the results.

4. The blood chemical components should not be altered by the procedure. This condition has been met for the components examined to date.

5. It must be possible to maintain sterility in the apparatus and in the technique of its use. This can be done, but when it was not, the results were not remarkably affected from the point of view of immediate survival.

6. Hemorrhage must be controlled after the use of heparin. A technique is presented which has proved adequate in most circumstances, experimental and clinical.

7. Emboli, gaseous or particulate, must not be pumped into the arterial tree. This condition has not been met, and probably was in great measure responsible for failure when it occurred. Although this has not been proved,

it may be a criticism to be leveled against oxygenators in which blood protein is exposed directly to oxygen, particularly those dependent upon bubble formation.

SUMMARY

1. Two types of oxygenators dependent upon the production of large easily broken bubbles are described. Each was found capable of fully oxygenating venous blood and at the same time adequately eliminating carbon dioxide from it. The larger Type II model is able to process up to 4,500 c.c. of blood per minute.

2. A pump without internal mechanical valves and actuated by positive and negative air pressure is presented. Of the pumps tested it was found the least traumatic to red cells and had the least tendency to form fibrin deposits.

3. Of seventy-four experiments in which the heart and lungs were excluded from the circulation for twenty-five minutes or more, there was an over-all mortality of 46 per cent. Included are a series of twenty consecutive experimental operations involving cardiotomy or incision into a great vessel with only one death.

4. Important among the causes of death which are reviewed were postoperative hemorrhage in fourteen animals and probable brain damage in nine animals manifested by low blood pressure during the total perfusion.

5. The results of hemodynamic, electrocardiographic, electroencephalographic, bacteriologic, and blood gas studies made during these perfusions in part confirm the suggestion that hypotension during perfusion, followed by death, resembles the normovolemic shock following experimental oligemic shock.

6. Data from three clinical perfusions are presented.

7. The criteria for the performance of successful prolonged total by-pass of the heart and lungs are reviewed. In these experiments all requirements were met with the exception of blood cell destruction and the production of arterial emboli, either gaseous or particulate.

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DISCUSSION

DR. KARL E. KARLSON (Brooklyn, N. Y.)—I would like to congratulate Dr. Clowes on this very intensive study. Dr. Dennis and I and our collaborators in the laboratory have been working on this problem for some time and have had all the headaches they had had and some extra ones.

In going over the reasons for the fatalities in the animals which Dr. Clowes presented, we understand that hemorrhage or fibrin formation was the cause of many of these fatalities. Bleeding after perfusion has been a problem in our laboratory, and it involves three factors: One is hemostasis at the time of operation, and this can be accomplished either by carefully ligating all the little bleeding points or using a cautery for this purpose. Either method is effective.

The second factor in bleeding is bacterial contamination, which occurred concurrently with hemorrhagic tendencies in our animals. The bacterium which we felt was the cause of this bleeding was a gram-negative rod, *Paracolobactrum intermedium.* We have now accomplished complete sterilization of our apparatus with autoclaving, and this syndrome has disappeared.

The third factor in hemorrhage is effective heparinization (which is necessary to prevent fibrin formation) and the incomplete neutralization of this heparin by protamine. We use 5 mg. of heparin per kilogram of body weight of the dog and 50 mg. of heparin per liter in the donor blood, an amount that is necessary to reduce fibrin formation in our apparatus to minimum levels. After perfusion we neutralize this heparin with protamine and find that we can do it effectively after establishing the dose of protamine by titrating the blood against known concentrations of protamine. After these three factors have been recognized, bleeding has not been a problem.

In regard to flow through the apparatus, we have found that the animals which are going to die have a drop in flow rate during perfusion. We have measured the peripheral resistance during perfusion and find that peripheral resistance increased in those animals that died. We have also demonstrated cerebral air embolization in the mortalities by inspecting the cerebral vessels. We think we prevent fibrin emboli, but air embolization is still a problem.

METABOLIC ALTERATIONS IN SURGICAL PATIENTS

III. The Influence of Peritonitis on Nitrogen, Carbohydrate, Electrolyte, and Water Balance*

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INTRODUCTION

FOR many years it has been recognized that profound alterations in normal body metabolism may occur in patients with peritonitis. In early classic descriptions of the patient with severe peritonitis it was noted that such patients exhibited sunken eyeballs, dry turgorless skin, distended quiet abdomen, rapid thready pulse, and scanty urine output. Bower, Terzian, and Pearce[1] in 1942 and subsequently others[2, 3] have emphasized the translocation of fluid rich in protein and electrolytes into the bowel and peritoneal cavity. Since the advent of chemotherapeutic agents and antibiotics, recent papers have been chiefly concerned with the efficiency of these drugs in the prophylaxis and treatment of peritonitis.

While the importance of proper water, electrolyte, and protein replacement therapy has been discussed in numerous clinical studies of this disease, a survey of the literature yields little information concerning the metabolic alterations in patients with peritonitis. The purpose of this study was to evaluate, by the balance technique, the metabolic alterations of fluid, sodium, chloride, potassium, and nitrogen in such patients. The patients were studied without attempting to alter the different regimens commonly employed. The parenteral alimentation used was not governed by the anticipated needs of the patient. This was done in order that we might secure information concerning the influence of therapy, as well as the disease, upon the rates and extent of retention or losses of the various nutrients. The water, electrolyte, and protein shifts which occur in patients with peritonitis forming a "third body fluid space"[4] are often comparable to changes which follow a second degree burn. As the infection subsides and the patient's condition improves, the remaining translocated substances are reabsorbed into the normal body fluid compartments. This reabsorption is frequently accompanied by a diuresis. The magnitude of these shifts is not only dependent on the disease process but is also influenced by the therapy. Observations were also made on these and other patients in the attempt to determine the extent and effect of these shifts. It was believed that this method of ap-

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proach would enable us to define and crystallize many of the underlying problems so that our continuing studies would make it possible for us to substantiate or refute a particular concept of parenteral alimentation designed to fit the needs of patients with peritonitis.

METHODS

Fifteen surgical patients were studied on the Metabolic Division of the University Hospitals of Cleveland.* These patients are divided into two groups: Group I consists of six patients who had perforation of the stomach or duodenum with peritonitis (five perforated peptic ulcers, one perforated gastric carcinoma). The second group consists of three patients with perforated appendicitis and peritonitis, two with acute salpingitis and pelvic peritonitis, one who developed peritonitis following a colectomy, two patients with appendiceal abscess, and one patient with perforation of a sigmoid diverticulum with peritonitis. The first twelve patients were operated upon, while the last three were treated without surgical intervention. Balance studies were started as soon as possible after admission. The techniques for collection, measurement, and chemical analysis have been reported in detail in a previous publication.[5]

The charting of the metabolic balances was done according to the method of Moore and Ball.[6] The intake, output, and the balance are plotted on the ordinate; the time is plotted on the abscissa. The intake is represented by the height of the column above the horizontal zero line, and output is plotted downward from the top of the intake column. Negative balance is indicated by extension of the column below the zero line, while the white area above the zero line represents a positive balance. When the patient was admitted as an emergency, his study was begun as soon as possible. Where the collection period was less than twenty-four hours, the first column shown was altered proportionally in width.

Four patients were given whole blood transfusions (400 to 1,000 ml.) at the time of operation. The nitrogen, sodium, chloride, and potassium content of blood was determined by making duplicate analysis.† However, these values were not included in the balance charts since the blood was given in amounts necessary to replace the estimated loss and because the rate of entrance into the metabolic pool of the substances in transfused blood is not known. The volume of blood given is indicated in the water balance by a broken line at the top of the intake column. Since no accurate method is available for determining the insensible fluid loss, which is dependent on many factors such as temperature, respiratory rate, and so forth, an estimated loss of 1,000 ml. per twenty-four hours was included as output and indicated in the fluid balance chart by a broken horizontal line below the measured fluid losses. While this is not an accurate measurement, it provides a better estimate of the total fluid losses which occurred. None of the patients in this group, except E. R., had significant amounts of wound drainage, and therefore no attempt was made to measure or analyze it.

All patients were given vitamins‡ intravenously or orally in amounts sufficient to exclude the metabolic effects of any possible vitamin deficiency.

RESULTS

In patients of Group I the peritonitis was mild and of short duration, and since operation was instituted early, it is difficult to distinguish the metabolic effects produced by the peritonitis from those due to the therapy. Fairly large amounts of sodium were being excreted in the urine (35 to 300 meq. per day)

*We wish to express our sincere gratitude to Helene Banta and Laura Silver, dietitians; Christine Lane and Callie Burnside, dietitians' helpers; Dorothy Freymeyer, R.N., Myrtle Edwards, R.N., Vida McKelvey, R.N., Kathleen Allen, R.N., Agnes Furman, R.N., Alice Stevulak, R.N., and also the laboratory staff, Jean Hower, Sophie Koenig, Ivan Madirazza, Doris Blum, Robert Gilman, Ingeborg Loesch, and Katherine Whiteside; and Evelyn Kocsis, secretary.

†Blood obtained from the blood bank had an average of 92 meq. of sodium, 36 meq. of potassium, 65 meq. of chloride, 17.5 Gm. of nitrogen per liter, and a hematocrit varying between 30 and 40 per cent.

‡Solu-Zyme and Unicaps kindly furnished by The Upjohn Company, Kalamazoo, Michigan.

by all the patients (Fig. 1). V. T. was given intraperitoneally at the conclusion of operation 500 ml. of normal saline solution containing Terramycin[7] and 1,000 ml. during the next twenty-four hours. Because of this and the fact that the patient had urinary retention during the first thirty-six hours, a positive balance of sodium and nitrogen occurred. She was then placed on constant

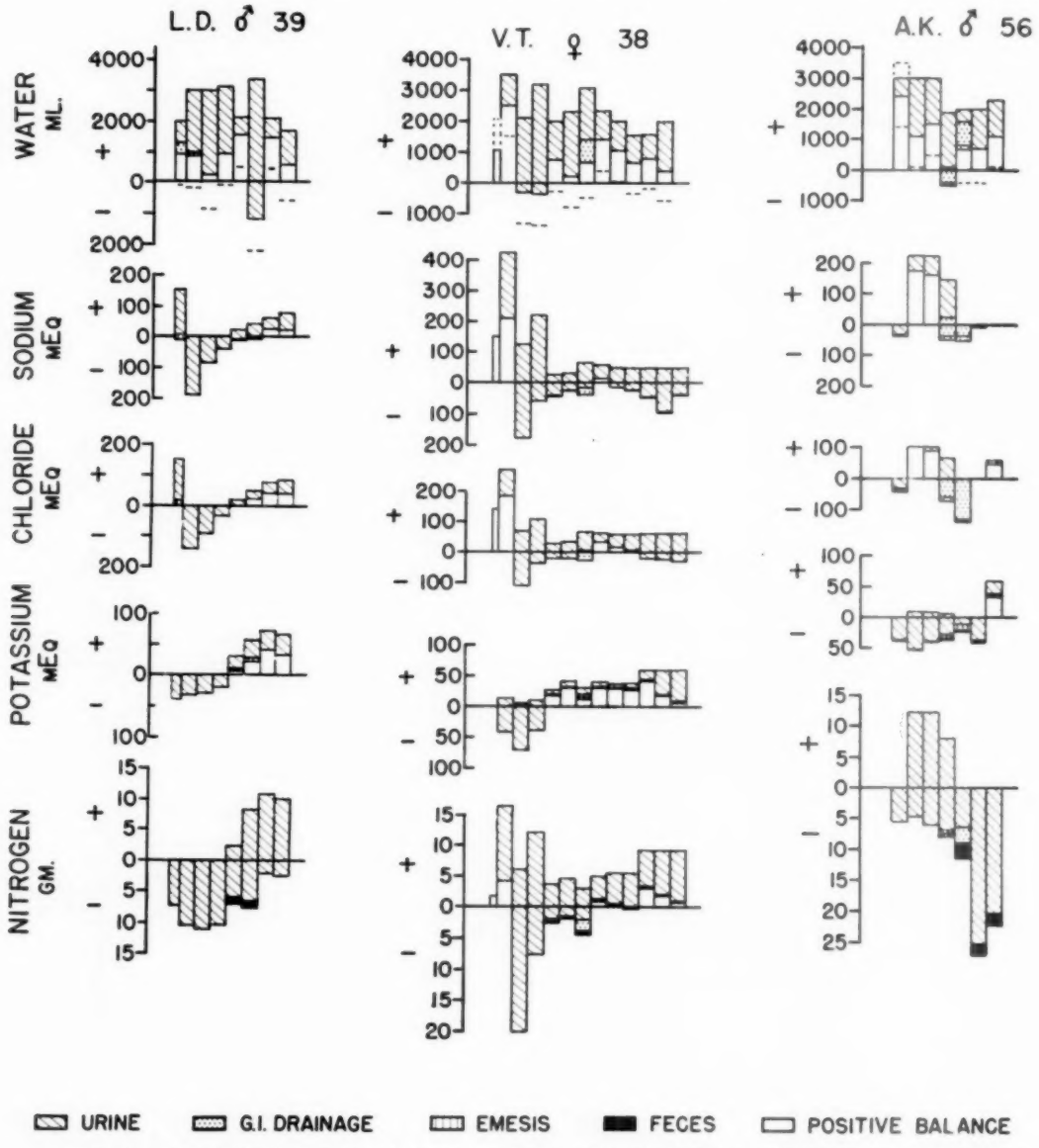

Fig. 1.—Metabolic balances of three patients with perforation of upper gastrointestinal tract and peritonitis (L. D., perforation of duodenal ulcer, V. T., perforation of gastric ulcer with hemigastrectomy and vagotomy, and A. K., perforation of gastric carcinoma).

urethral drainage and exhibited a marked negative balance of these substances. It is therefore believed that the retention of water, sodium, and chloride during the first and second collection periods resulted from: (1) the fact that these substances were not available for immediate excretion[8] and (2) the fact that after excretion they were retained in the bladder. This assumption is borne out by

the elimination of water, nitrogen, and electrolytes on the third study day. The water, sodium, and chloride retention shown by A. K. during the second and third days can be explained by a previous deficit of water and electrolytes. In contrast to the other patients, he had a poor intake coupled with increased losses for several days prior to admission and a zero intake of these ions on the first day of study. The output of chloride (2.2 meq.) on the sixth day and sodium (3.6 meq.) on the seventh day for Patient A. K. were so small that they could not be plotted.

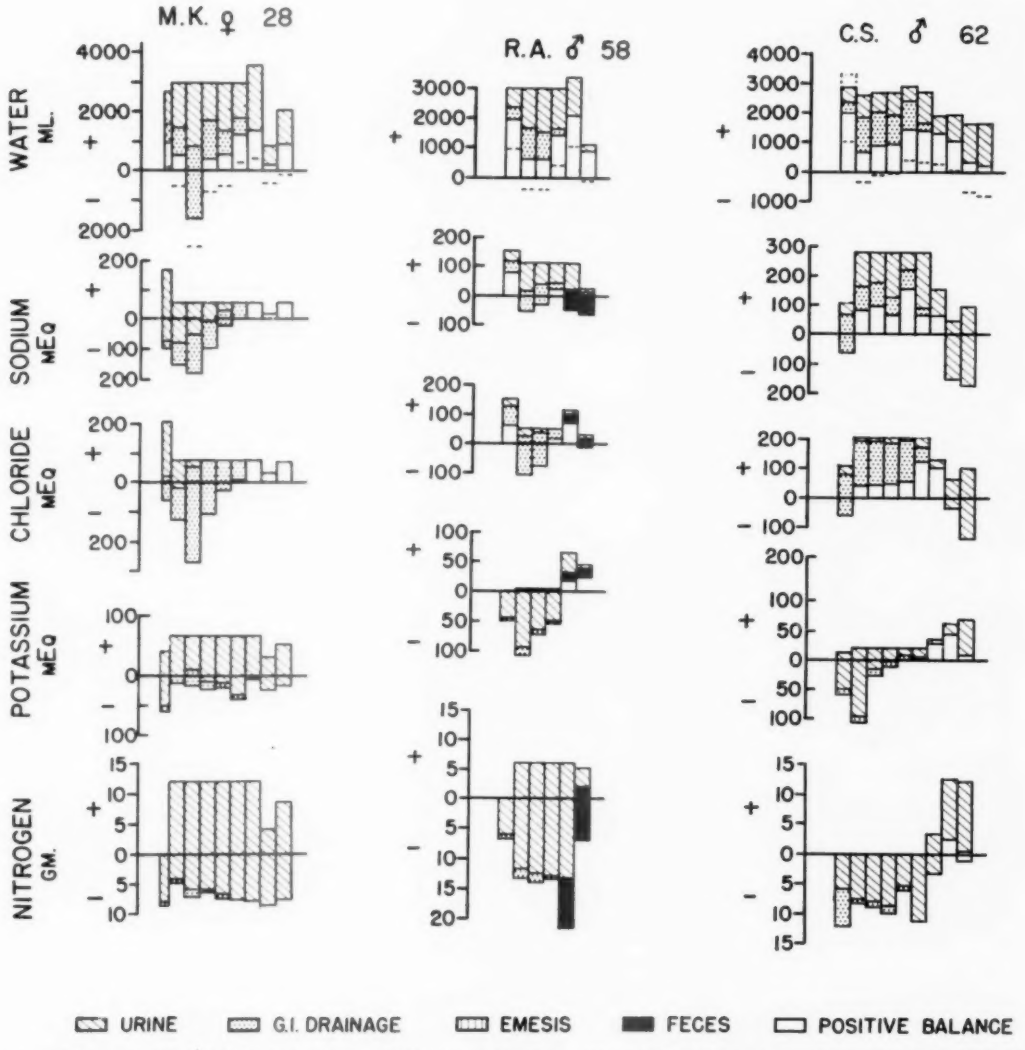

Fig. 2.—Metabolic balances of three patients with perforation of upper gastrointestinal tract and peritonitis (M. K., perforation of duodenal ulcer, R. A., perforation of duodenal ulcer, and C. S., perforation of gastric ulcer).

The relatively large urinary sodium excretion noted in patients M. K., R. A., and C. S. (Fig. 2) might be the result of the increased chloride losses via the gastric drainage. It should be noted that urinary loss of chloride was slight in comparison to the amount of sodium excreted by the kidney in these three patients. The cumulative deficits of potassium in these patients, while not large, was greatest when little or no intake of this ion occurred. M. K., who received

the largest amounts of potassium, showed a cumulative potassium deficit for the first six and three-quarters days of 178 meq. Such a deficit frequently occurs when a large amount of fixed base is excreted by the kidneys in response to a loss of gastric secretions containing a large amount of chloride. This deficit might have been prevented had larger amounts of fixed base been administered.

Negative nitrogen balance was most marked in patients who had a low or zero nitrogen intake or who lost fairly large amounts of fixed base. It is known that the caloric intake in all patients of this group was insufficient to exert any significant nitrogen-sparing effect.

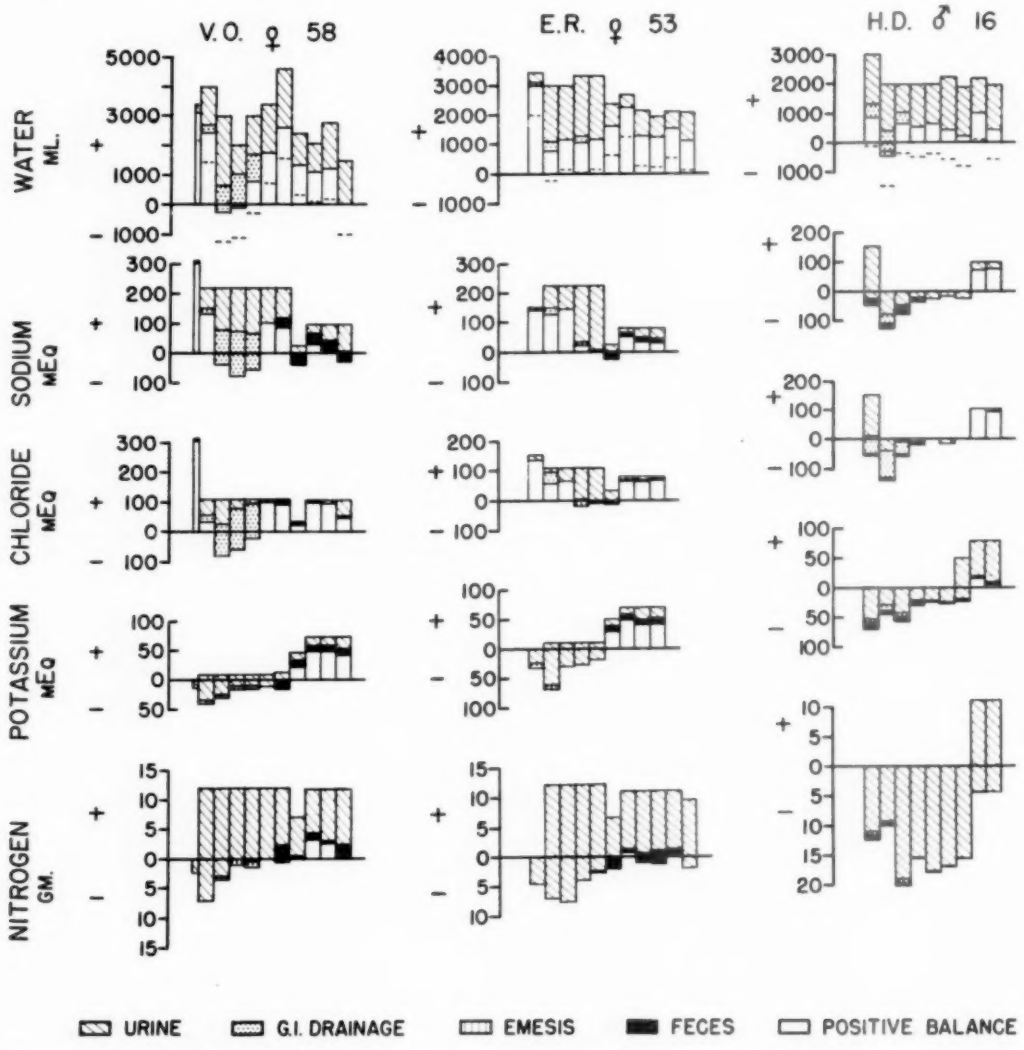

Fig. 3.—Metabolic balances of three patients with appendicitis with perforation and peritonitis.

Figs. 3, 4, and 5 show the metabolic balance studies in the second group of patients. All of these individuals were on an average daily fluid intake of 2,500 to 3,000 ml. In five patients the sodium intake was relatively large (100 to 200 meq. per day) during the study period. The other three patients received little or no sodium until the last two or three days. The chloride intake (50 to 100 meq. per day) was comparable except that the amount was approximately

one-half that of sodium. The potassium intake was zero in four of the patients (H. D., F. Y., V. P., and K. G.) during the first three to eight days. The other five patients received 5 to 85 meq. daily for five to seven days. In four patients the nitrogen intake was zero during the first three to nine days. The others received between 6 and 12 Gm. of nitrogen during the period of study. Continuous gastric suction was employed in six of the patients for two to eight days. Only three patients, V. O., H. D., and W. C., had significant volumes of drainage.

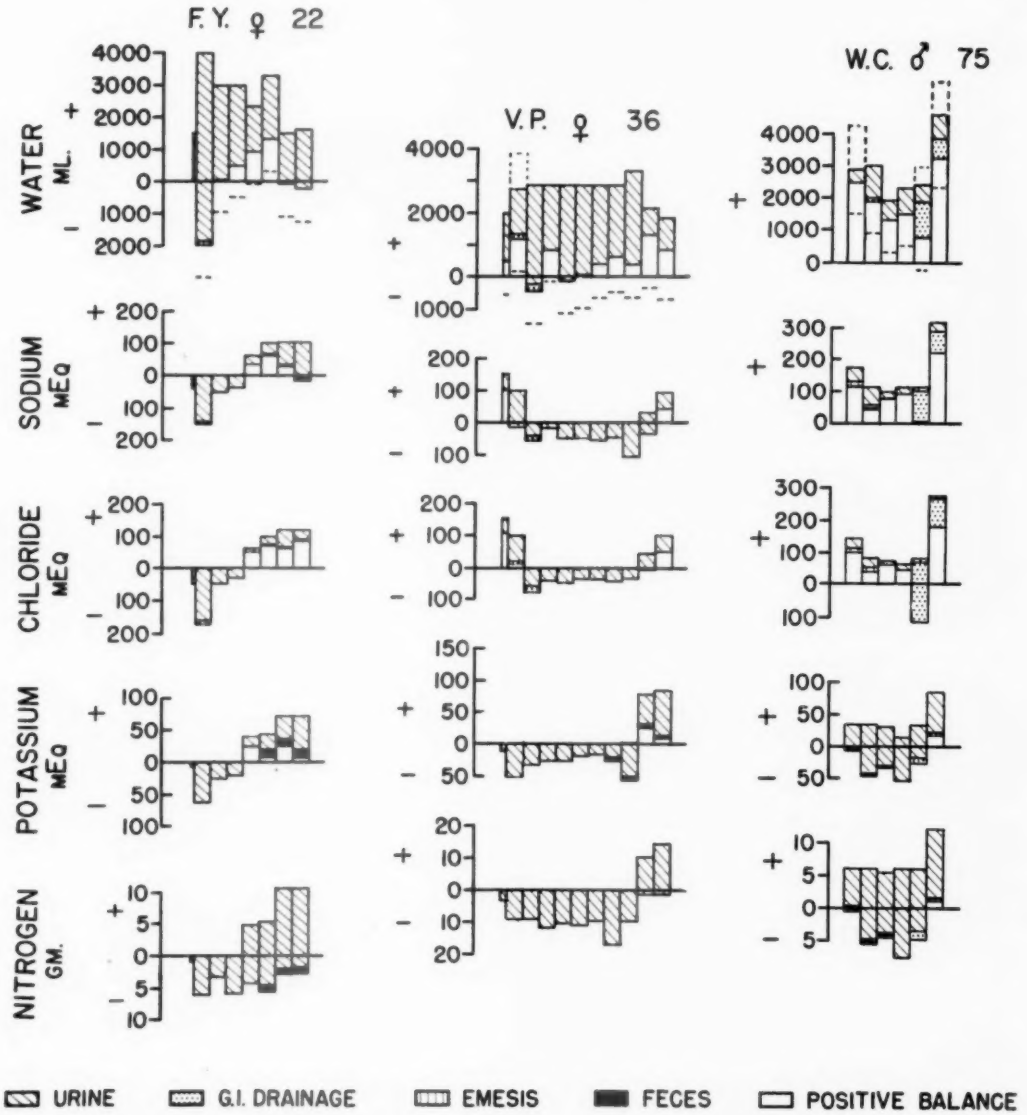

Fig. 4.—Metabolic balances of two patients (F. Y. and V. P.) with acute salpingitis and pelvic peritonitis and one patient (W. C.) with peritonitis due to ischemic necrosis of a segment of small intestine following resection of the right colon.

Three patients, V. O., E. R., and H. D., whose balance studies are shown in Fig. 3, had acute appendicitis with perforation and peritonitis. The time from onset of illness until operation was four, one and one-half, and two days, respectively. V. O. and E. R., two women of approximately the same age, were in

good health until the onset of their acute illness. They were moderately obese, weighing on admission 73.1 and 82.5 kilograms, respectively. The daily fluid, sodium, potassium, chloride, and nitrogen intakes were approximately the same for the two patients. Except for the day of admission, electrolyte and nitrogen intake was attained by the daily intravenous administration of 2,000 ml. of a 5 per cent plasma hydrolysate in 5 per cent dextrose.* E. R. had a daily

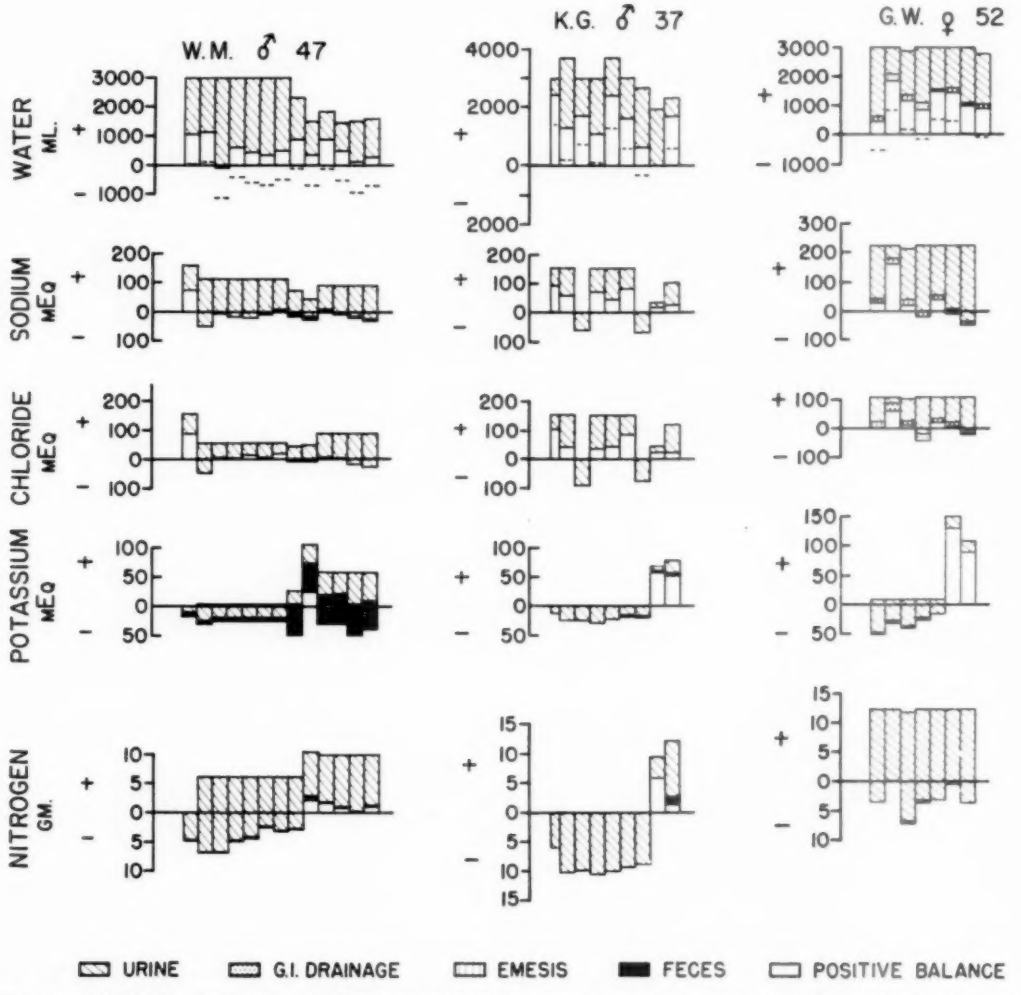

Fig 5.—Metabolic balances of two patients with appendiceal abscess (W. M. and K. G.) and one patient with diverticulitis with perforation and peritonitis (G. W.).

average carbohydrate intake of 214 Gm., and a caloric intake of 18 calories per kilogram per day. V. O. had a daily average carbohydrate intake of 146 Gm. and a caloric intake of 15 calories per kilogram per day. The metabolic balances in these two patients, especially for the first five days, may be compared. During the first two days, both patients retained water and sodium. Thereafter, for the next three days V. O. was in negative sodium and water balance. During this period there were moderately large volumes of fluid removed by gastrointestinal suction (850 to 1,130 ml. per day), which contained 115 to 154 meq. of sodium

*Travamin (containing 112 meq. of sodium, 54 meq. of chloride, 5 meq. of potassium, and 6.12 Gm. of nitrogen per liter) was kindly furnished by Baxter Laboratories, Inc., Morton Grove, Illinois.

per day. Only small to moderate amounts of peritoneal fluid drained from the incision. On the sixth day the volume of tube drainage decreased to 10 ml. and good peristaltic sounds were heard. On this day and the day after, both sodium and water were retained, presumably to replace deficits incurred during the preceding three days. From the eighth day on, the patient's intake was entirely by the oral route. It should be noted that for the last five days of the study, the feces, which were soft and watery, contained approximately 40 meq. of sodium per day. This higher-than-normal fecal sodium loss also occurred in other patients who had soft or watery stools. Chloride balance, in general, paralleled that of sodium. Renal conservation of chloride became more pronounced as gastrointestinal fluid losses increased. This was comparable to the findings in some of the patients in Group I. During the first seven days, V. O. showed a gradually diminishing daily potassium deficit. With an oral intake of 47 to 73 meq. of potassium, large amounts of this ion were retained, and a marked positive balance occurred for the remainder of the study. On a constant daily intake of 12.24 Gm. of nitrogen, there was only a moderate negative nitrogen balance with a progressively decreasing daily deficit, and equilibrium was reached on the sixth day. At this time, the patient's temperature and intestinal motility were normal, and wound drainage and gastrointestinal fluid loss negligible. As mentioned previously, this patient's caloric intake was only 15 calories per kilogram per day. The patient lost 2.25 kilograms between the second and the sixth day but maintained her weight within 0.3 kilogram thereafter. A possible explanation for the minimal nitrogen losses is the utilization of endogenous fat, thus sparing protein as a source of energy.

At the time of operation, E. R. had a more severe peritonitis, and subsequently a more fulminating course than V. O. Her temperature fluctuated between 38.5° and 37.5° C. during the ten-day study period. For six days, copious amounts of serosanguineous fluid came from around the Penrose drain which had been inserted at the time of operation. These differences in severity of illness are reflected in the two balance studies. Except for the first day, E. R. was in equilibrium or had a slightly positive water balance. In contrast to V. O., she had a moderately large positive sodium balance during the first three days. Although this patient was on continuous gastric drainage for four days, only negligible amounts of fluid were obtained. During this same period there were significant amounts of fluid draining from the peritoneal cavity which could not be recovered for analysis but could have caused a negative water, sodium, and chloride balance and still greater losses of potassium and nitrogen. The chloride balance is comparable to that of sodium. A gradually diminishing daily negative potassium balance occurred while this patient was receiving 0 to 10 meq. of potassium per day. When 50 to 75 meq. of potassium was given beginning on the sixth day, a large positive balance immediately occurred. Although she was on the same daily nitrogen and potassium intake and received more calories than V. O., E. R. exhibited a larger daily nitrogen deficit. The nitrogen loss would have been greater if wound drainage had been measured. While these balance studies do not show losses due to wound drainage, this may have been a very significant route for the loss of water, electrolytes, and nitrogen.

H. D., a previously healthy 16-year-old boy, had copious amounts of thin purulent peritoneal fluid at operation. Since no drains were left in the wound, the fairly large losses of water, sodium, chloride, and nitrogen could be accounted for, in part, by reabsorption of these substances from the peritoneal cavity and ultimate excretion. When electrolytes and nitrogen were given, electrolyte balances immediately became positive, and the nitrogen deficit was significantly decreased. It is interesting to note that during the period of negative electrolyte balance, all serum electrolyte concentrations were within the normal range.

In Fig. 4 are shown the metabolic balances of F. Y. and V. P. These were two young women with mild to moderate pelvic inflammatory disease who underwent operation. For the first three to seven postoperative days the only intake in both patients was daily intravenous infusions of hexose in water. During this period, both were in negative water, electrolyte, and nitrogen balance. The renal conservation of electrolytes with no intake is demonstrated by the gradual daily decrease of sodium, chloride, and potassium in the urine of F. Y. With the administration of electrolytes and nitrogen, a positive electrolyte balance resulted and nitrogen deficits were significantly diminished.

The balance studies of W. C. are shown in Fig. 4. On the first study day, this 75-year-old man had a right colectomy for a large perforating carcinoma of the ascending colon. The second day, the patient did well clinically and had no complaints. On the third day, he complained of abdominal pain; peristaltic sounds, which had been present earlier in the day, were diminished; and the abdomen became slightly distended. The temperature and white count gradually increased. It should be noted that there was an increased retention of water, sodium, and chloride on this day. During the next two days, the patient's symptoms became more severe, and he had early signs of peritonitis. On the fourth day, there was further retention of water, sodium, and chloride. On the fifth day, a large volume of gastric drainage was obtained which accounted for the increased sodium and chloride losses. On the sixth day, he was reoperated upon, and a four-foot segment of gangrenous small bowel (due to an embolus in a branch of the superior mesenteric artery) was resected. The peritoneal cavity contained a large amount of bloody fluid which was cultured (Staphylococcus, Streptococcus, *Clostridium welchii*, paracolon). The bowel was distended and there were moderate edema and inflammation of the mesentery, peritoneum, and bowel wall. The patient tolerated the operation without difficulty and was doing exceptionally well until the evening of the first postoperative day, when he suddenly died from acute occlusion of both coronary arteries (demonstrated at autopsy). This study demonstrates the increased retention of water, sodium, and chloride and a greater nitrogen loss in the presence of a large "third fluid compartment" which could be observed at the time of the second operation.

The balance studies of K. G. and W. M., each of whom had an appendiceal abscess, and G. W., who had peritonitis resulting from the perforation of a sigmoid diverticulum, are shown in Fig. 5. Since these three patients were treated without operation, the alterations in their metabolic balances were not influenced by the additional stress associated with a surgical operation. W. M., who had been ill for two weeks, complained on admission of anorexia and right lower quadrant pain. A 15 cm. mass which was thought to be an abscess was present. The patient's temperature, which was 38.5° C. on admission, rose to 39° C. on the day after admission and then rapidly fell to normal and remained there for the rest of the hospital stay. At the time of the temperature fall, the mass decreased dramatically in size and then gradually disappeared. On the day of admission the patient was given 2,000 ml. of 10 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. On this day, the water balance was essentially in equilibrium. Sodium and chloride were retained, possibly because of a deficit which had occurred prior to admission. A negative potassium and nitrogen balance occurred on this day. For the next six days he was given a daily infusion of 1,000 ml. of a 5 per cent plasma hydrolysate in 5 per cent dextrose and 2,000 ml. of 10 per cent dextrose in water. This regimen supplied a daily sodium intake of 112 meq. and a chloride intake of 54 meq. During these six days the daily urine volume was large and the patient was in equilibrium or negative fluid balance. Sodium and chloride were

excreted in the urine in fairly constant amounts (100 and 50 meq., respectively), and the balance of these constituents showed only slight fluctuations from equilibrium. The daily fecal sodium and chloride losses were less than 0.5 meq. per day. With a daily intravenous intake of 5 meq. per day, 20 to 27 meq. of potassium was lost in the urine. The serum electrolyte concentrations on the second day were sodium 129, chloride 85, and potassium 3.6 meq. per liter and on the fourth day 136, 97, and 4.7 meq., respectively. On the last day of the study the serum electrolyte concentrations were essentially unchanged. The nitrogen intake was 6.13 Gm. per day with a caloric intake of 18 calories per kilogram per day. The daily loss of nitrogen in the urine gradually decreased, but nitrogen balance remained negative throughout the six-day period.

K. G., who had been ill for nine days, was severely dehydrated and had a temperature of 39.5° C. on admission. For five days he received daily intravenous infusions of 5 per cent dextrose in water and 5 per cent dextrose in normal saline solution except for the third study day, on which only dextrose in water was given. During these five days the patient was febrile with a temperature fluctuating between 38° C. and 40° C. He had a retention of water, sodium, and chloride and a positive balance of these substances except on the two days when the sodium and chloride intake was zero. Potassium was excreted in the urine at the rate of 13 to 27 meq. per day. When 68 meq. of potassium was given on the ninth day, a positive balance of 50 meq. occurred. Approximately 10 Gm. of nitrogen per day was lost in the urine, but positive balance resulted following the administration of 12 Gm. of nitrogen on the ninth day. In this patient no results were included for the eighth day since some of the excreta were accidentally spilled.

G. W. received 1,000 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution shortly after admission, fourteen hours prior to beginning the study. This is not shown on the balance chart since metabolic studies were not started until the following morning. For the following eight days she was given a daily intravenous infusion of 2,000 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose and 1,000 ml. of 10 per cent dextrose in water. On the first day of the study a large volume of urine was excreted, resulting in a negative water balance, while sodium balance was positive by 20 meq. The next two days, water, sodium, and chloride balances were all positive. During this three-day period the patient had a moderately severe ileus with distention and hypoactive peristaltic sounds. Only 100 to 200 ml. of gastrointestinal contents drained daily through the long intestinal tube. On the fourth day, intestinal motility increased and the distention diminished following the passage of flatus. An increased urine volume on this day was accompanied by a larger loss of sodium and chloride. With a potassium intake of 10 meq. per day, there was a cumulative deficit of 161 meq. in five days. When 150 meq. of potassium was given on the sixth day there was a positive balance of 130 meq., and the following day a retention of 88.5 meq. occurred with administration of 110 meq. of potassium. The nitrogen intake was 12.3 Gm. per day and the caloric intake 24 calories per kilogram per day. The cumulative nitrogen deficit for the seven days was 21.4 Gm. or an average deficit of 3.0 Gm. per day. A second metabolic study was carried out when she was readmitted six weeks later for a resection of the sigmoid colon. On this occasion she had a daily caloric intake of 27 calories per kilogram and received no nitrogen, sodium, chloride, or potassium for five days. Studies made at this time showed a five-day cumulative deficit of 218 meq. of sodium, 244 meq. of chloride, 134 meq. of potassium, and 35.1 Gm. of nitrogen. While the patient sustained the stress of an operation, no infection was present and she did not appear as ill at this time as on the previous admission. Although

the two studies are not entirely comparable, it is interesting to note that greater deficits of sodium, chloride, potassium, and nitrogen (average daily loss of 7 Gm.) occurred following the operation than when only peritonitis was present.

A comparison of two balance studies on Patient W. M. showed results somewhat similar to those exhibited by G. W. When W. M. was observed for seven days with a large appendiceal abscess and was given intravenously 18 calories per kilogram, including 6.1 Gm. of nitrogen, he showed a cumulative deficit of 33.3 Gm. of nitrogen (average daily negative nitrogen balance of 4.76 Gm.), as compared to a five-day cumulative deficit of 37.1 Gm. of nitrogen (average daily deficit of 7.42 Gm.) following an interval appendectomy. In G. W. the caloric intake was comparable in the two studies, but W. M. received considerably fewer calories per kilogram on the second admission.

DISCUSSION

When this investigation was started it was hoped that patients with severe peritonitis could be studied, but no patients of this type were available. It should also be pointed out that alterations due to the stress of operation cannot be clearly delineated from those which were the result of peritonitis except in W. M., K. G., G. W., and W. C. In these nonoperated patients the magnitude of the alterations appeared to depend on the extent and duration of infection. In those cases where infection was brought under control, the metabolic abnormalities subsided rapidly. In some of the patients (Group I), changes appeared to be comparable to those associated with operation alone.

Three important factors which influence the metabolic alterations in peritonitis are:

1. Severity and duration of the adynamic ileus.
2. Extent and degree of peritoneal inflammation.
3. Systemic response to infection and complications.

These will be discussed with respect to the alterations in water, mineral, and nitrogen metabolism.

Adynamic ileus may produce biochemical changes comparable to those in mechanical intestinal obstruction. Essentially there are two mechanisms which result in the diversion of varying amounts of water, electrolyte, and protein from the extra- and intracellular compartments. One is the failure of normal reabsorption of water and electrolytes from the intestinal tract. The other is the translocation of water, electrolytes, and protein associated with inflammation and/or distention. A review of the literature leads one to the opinion that continued secretion of gastrointestinal fluid and interference with reabsorption occurs until the intraluminal pressure of the bowel increases to the point where capillary flow is diminished or stopped, at which time secretion ceases.[9, 10] Gatch and Battersby[10] observed in animals a "sweating of albuminous fluid from the peritoneal surface of the distended intestine," when the distention was great enough to arrest intramural blood flow and stop secretions. They also noted that the bowel became markedly edematous and cyanotic after the distention was released. Analysis of the fluid which they collected from the peritoneal cavity revealed an average protein concentration

of 3.6 Gm. per 100 ml. with an albumin content of 2.6 Gm. per 100 ml. Analysis of peritoneal fluid from three patients not included in this study showed average concentrations (per liter) of 138 meq. of sodium, 105 meq. of chloride, 4.93 meq. of potassium, and a nitrogen concentration which ranged from 2 to 12 Gm. per liter. It has been shown that blister fluid obtained from patients following a thermal injury had the following composition: sodium 136.5, chloride 96.2, potassium 5.18 meq. per liter, and albumin 3.76 Gm. per 100 ml. These values are very similar to average concentrations in the peritoneal fluid mentioned previously. The fluid which accumulates in the peritoneal cavity in the presence of inflammation and infection is therefore not unlike that which is lost in a second degree burn.

Various workers[12, 13] have demonstrated that there is a significant decrease in plasma volume associated with distention of the bowel. In 1939, Gendel and Fine[12] reported an average decrease of 36.4 per cent in the plasma volume of dogs after four to six hours of distention of a long segment of small bowel obstructed at both ends. After twenty-four hours of distention a 55 per cent decrease in plasma volume was reported. In patients with intestinal obstruction, Fine, Hurwitz, and Mark[13] demonstrated plasma volume increases of 1,000 ml. or more, following decompression of the intestine.

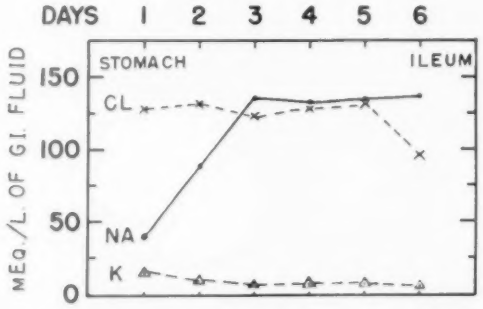

Fig. 6.—The sodium, potassium, and chloride concentration of gastrointestinal fluid as a long intestinal tube advances down the gastrointestinal tract.

Bower, Terzian, and Pearce[1] showed in dogs with spreading peritonitis an average decrease of 21.5 per cent in the plasma volume and 14.9 per cent in the total circulating plasma protein. Ebert, Hagen, and Borden[14] demonstrated an average plasma volume reduction of 44 per cent in five untreated dogs with peritonitis. After death, 55 to 350 ml. of fluid with an average protein content of 2.5 Gm. per 100 ml. was found in the peritoneal cavity of these animals.

In those patients who are on continuous suction, the electrolyte composition of the fluid which is lost from the body varies with the level in the gastrointestinal tract at which the fluid is being aspirated, as well as the disease of the patient and the type of treatment. Fig. 6 shows the concentration of sodium, chloride, and potassium in the suction fluid obtained at various levels as a long intestinal tube advanced down the gastrointestinal tract of a distended patient. The sodium concentration of the aspirated fluid increased from 40 meq. per liter when the tube was in the stomach to 136 meq. per liter when it reached the terminal ileum, while at the same time the chloride concentration decreased

from 129 to 96 meq. per liter. These values are within the same range as those reported by Randall,[4] although in most of his patients and in others we have studied, the average sodium concentration in gastric fluid has been 60 to 90 meq. per liter. An example of this difference in electrolyte composition can be seen if the drainage fluid from the stomach of A. K. is compared with the fluid obtained from the mid-portion of the small intestine of V. O. In the former case the average electrolyte concentrations were sodium 65 meq. and chloride 108 meq. per liter, while in the latter they were sodium 136.6 meq. and chloride 125.4 meq. per liter. This significant variation should be kept in mind when planning replacement therapy for the patient who is on gastrointestinal drainage, as emphasized by Randall.[4]

Fig. 7 shows the concentration of sodium, chloride, and potassium in fluid from various sources in the body which may be permanently or temporarily lost from the extracellular fluid compartment. The individual values have been obtained in our studies, while the ranges are those reported by various authors. It should be noted that the values for sodium and chloride in peritoneal fluid and wound exudate are approximately the same concentration as in extracellular fluid. Potassium concentration and that of nitrogen, which is not shown, may vary considerably, depending on the amount of blood, leukocytes, and necrotic tissue present.

THE SODIUM, POTASSIUM, AND CHLORIDE CONTENT OF VARIOUS BODY FLUIDS EXPRESSED IN MILLIEQUIVALENTS PER LITER. THE VALUES FOR WOUND EXUDATES WERE OBTAINED FROM UNPUBLISHED DATA ON PATIENTS WITH THERMAL BURNS, WHICH WERE SUPPLIED BY ONE OF US (W. E. A.)

SOURCE OF FLUID	Na	Cl	K
	(MEQ. PER LITER)		
Stomach	60 (20-120)	129 (40-140)	10 (4-15)
Ileum	136 (90-145)	96 (80-115)	7.3 (4-20)
Peritoneal cavity	138 (130-140)	105 (90-110)	5 (3-10)
Wound exudate	139 (120-150)	104 (90-112)	5 (2-50)

Fig. 7.

Potassium and nitrogen losses in gastrointestinal drainage were relatively small in the group of patients under discussion, but in those patients who had diarrhea, larger amounts of potassium were lost in the stool. Darrow[15] has discussed the significance of the loss of potassium resulting from diarrhea and the importance of its replacement.

The results of our studies demonstrate that the renal losses of water and fixed base which occur as compensation for the extrarenal losses can be a significant factor in the production of dehydration. This was best demonstrated by M. K., who, because of large losses of chloride in the gastric fluid, responded by excreting significant amounts of water, sodium, and potassium by way of the kidneys. The reduced intake, vomiting, and the translocation of water, minerals, and protein into the gastrointestinal tract and peritoneal cavity largely account

for the plasma and interstitial fluid volume deficits which are seen in patients with peritonitis. Another important factor is the acceleration of body catabolism associated with inflammation and infection. Madden and Clay[16] made nitrogen balance studies before and after the production of a turpentine abscess in dogs. They found that an increased catabolism of protein was responsible for an accelerated loss of nitrogen in the urine, and they were able to reduce the nitrogen deficit by supplying large amounts of protein. Our studies over the past two and one-half years are in agreement with these findings. A comparable situation is seen if one compares the nitrogen balances of V. O. and H. D. (Fig. 3). Both patients lost large amounts of nitrogen in the urine, indicating the increased protein catabolism associated with their peritonitis. V. O., who received large amounts of nitrogen in the form of amino acids, showed a much smaller negative nitrogen balance than H. D., who had a zero nitrogen intake for the first seven days. Likewise, G. W. and W. M. showed much greater nitrogen losses on their second admission, when they were not given amino acids. The increased loss of potassium in the urine and negative balance which occurs in patients with peritonitis is the result of several factors. Fenn,[17] in 1940, demonstrated that a breakdown of glycogen and tissue protein was associated with a discharge of potassium from the cells. This undoubtedly accounts for much of the potassium loss, but a significant amount can be lost, as emphasized by Elkinton and Winkler[18] who stated that "loss of intracellular potassium in excess of that associated with protein catabolism is a general response to water depletion from any cause." In 1952, Black and Milne[19] demonstrated the progressive renal conservation of potassium in normal subjects on a low potassium intake. Evidence of this renal conservation is seen in present patients and was reported in a previous study.[5] It was also noted by Black and Milne[19] that when potassium is given in fairly large amounts, more is often retained than is lost. Thus, it is erroneous to conclude that the extent of positive balance of this cation during the repletion period is a measure of the amount lost.

CONCLUSIONS

1. The metabolic alterations of water, sodium, chloride, potassium, and nitrogen balance which occur in peritonitis are largely dependent on the severity and duration of the disease and the type of replacement therapy.

2. The two most important factors in the etiology of these alterations are adynamic ileus, and the accumulation of electrolyte- and protein-containing fluid in the peritoneal cavity. In both instances water, electrolytes, and protein are shifted into the third body fluid space, at the expense of the extracellular compartment.

3. In planning fluid, electrolyte, and nutritional therapy the following factors must be considered.

(a) The volume and composition of fluid lost from the gastrointestinal tract.

(b) Wound drainage.

(c) Deficits which might result from renal losses, internal shifts of fluid, electrolyte, and protein into the peritoneal cavity and bowel wall or lumen.

(d) Accelerated nitrogen loss associated with increased protein catabolism and additional calories to satisfy increased metabolic needs.

CLINICAL COURSE OF PATIENTS PRESENTED

CASE 1.—L. D., a 39-year-old Negro man, was admitted with a three-hour history of epigastric pain and vomiting. Seven hours after admission, a perforated duodenal ulcer was plicated under gas-oxygen-ether anesthesia. The patient received 1,000 ml. of 5 per cent dextrose in normal saline solution and 1,000 ml. of 5 per cent dextrose in water on the day of operation. For the next three days he was maintained on intravenous infusions of 5 per cent dextrose in water. Oral feedings were started on the fourth postoperative day. The temperature ranged from 36.5° to 38.2° C.

CASE 2.—H. D., a 16-year-old Negro man, was admitted with a two-day history of abdominal pain, vomiting, and diarrhea. A perforated appendix was removed under spinal anesthesia. The patient received 1,000 ml. of 5 per cent dextrose in normal saline solution and 2,000 ml. of 5 per cent dextrose in water on the day of operation. For the next six days he was maintained on intravenous infusions of 5 per cent dextrose in water. Water by mouth was allowed on the fifth and sixth days, and on the seventh day oral feeding was started. The temperature ranged from 37.0° to 39.7° C.

CASE 3.—V. O., a 58-year-old white woman, was admitted with a four-day history of abdominal pain and vomiting. A gangrenous appendix was removed under gas-oxygen-ether anesthesia. The patient received 2,000 ml. of 5 per cent dextrose in normal saline solution and 1,400 ml. of dextrose in water on the day of operation. Forty milliequivalents of KCl was added to these fluids. For the next six days she was maintained on daily intravenous infusions of 2,000 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose and 1,000 to 2,000 ml. of 5 per cent dextrose in water. Oral feeding was started on the seventh day. The temperature ranged from 36.5° to 38.5° C.

CASE 4.—W. M., a 47-year-old Negro man, was admitted with a two-week history of abdominal pain, a tender mass in the right lower quadrant, fever, and leukocytosis. A diagnosis of appendiceal abscess was made, and the patient was treated without operation with rapid regression of the abscess. On the day of admission the patient received 2,000 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. For the next six days he was maintained on daily intravenous infusions of 1,000 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose and 2,000 ml. of 10 per cent dextrose in water. Oral feedings were started on the seventh day. The temperature ranged from 36.5° to 39° C. The patient was readmitted two months later for interval appendectomy.

CASE 5.—V. T., a 37-year-old white woman, was admitted with a four-week history of intermittent epigastric pain with nausea and vomiting on two occasions. On the day of admission the patient had severe generalized abdominal pain with persistent nausea and vomiting. Six hours after onset, the patient was taken to surgery, where a perforated gastric ulcer was found which obstructed the pylorus when closure was attempted. For this reason, a hemigastrectomy, gastroduodenostomy, and vagotomy were performed, under endotracheal gas-oxygen-ether anesthesia. The patient received 1,000 ml. of whole blood and 1,500 ml. of normal saline solution during the operation. In addition, on the day of operation she received 2,700 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose. For the next six days intravenous infusions consisting of 5 per cent protein hydrolysate in 5 per cent dextrose (two days) and 5 per cent dextrose in water (six days) were given. Oral fluids were started on the second postoperative day. The temperature ranged from 37° to 38.7° C.

CASE 6.—F. Y., a 22-year-old Negro woman, was admitted with a three-hour history of right lower quadrant pain. Three hours after admission the patient was taken to surgery, where an operative diagnosis of acute salpingitis and pelvic peritonitis was made. Appendectomy was performed. On the day of operation and for the next two days the patient was maintained on intravenous infusions of 5 per cent dextrose in water. Oral feedings were started on the third postoperative day. The temperature ranged between 37° and 38.5° C.

CASE 7.—E. R., a 53-year-old white woman, was admitted with a thirty-hour history of abdominal pain and one episode of vomiting. The patient was taken to surgery shortly after admission, where a perforated appendix and diffuse suppurative peritonitis were found at operation. On the day of operation the patient received 2,400 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. For the next four days intravenous infusions consisting of 2,000 ml. of 5 per cent amino acids in 10 per cent invert sugar (Travert) and 1,000 ml. of 10 per cent invert sugar were given. Oral feedings were started on the third postoperative day. The temperature ranged from 37° to 38.8° C.

CASE 8.—R. A., a 58-year-old white man, was admitted with a three and one-half hours' history of severe abdominal pain and a single episode of vomiting on each of the two preceding days. The patient had been treated with a medical regimen for duodenal ulcer for six years. Five hours after admission a perforated peptic ulcer was plicated under spinal anesthesia. On the day of operation the patient received 2,000 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. For the next four days the patient received daily intravenous infusions of 2,000 ml. of 10 per cent fructose and 1,000 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose. Oral feedings were started on the fourth postoperative day. The temperature ranged from 37° to 39° C. The postoperative course was complicated by a right lower lobe pneumonitis.

CASE 9.—K. G., a 37-year-old white man, was admitted with a nine-day history of abdominal pain, anorexia, a tender mass in the right lower quadrant, fever, and leukocytosis. A large appendiceal abscess could be palpated. The patient was treated without surgical intervention. After four days of high fever, the abscess mass resolved and the temperature returned to normal overnight (39.6° to 36.8° C.). For the first two days the patient was given a daily intravenous infusion consisting of 2,000 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. The third day he received 3,000 ml. of 5 per cent dextrose in water. For the next three days he again was given 2,000 ml. of 5 per cent dextrose in water and 1,000 ml. of 5 per cent dextrose in normal saline solution. Oral feedings were started on the seventh hospital day. The temperature fluctuated between 38° and 40° C. for the first four days. Thereafter it was normal.

CASE 10.—M. K., a 28-year-old white woman, was admitted with a three-hour history of severe epigastric pain without nausea or vomiting. For two months prior to admission the patient had had typical peptic ulcer symptoms. Four hours after admission a perforated pyloric ulcer was plicated under spinal anesthesia. On the day of operation the patient received 1,100 ml. of normal saline solution, 1,000 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose, and 600 ml. of 5 per cent dextrose in water. For the next six days the patient was maintained on daily intravenous infusions of 2,000 ml. of 5 per cent casein hydrolysate in 5 per cent dextrose* and 1,000 ml. of 10 per cent dextrose in water. Oral fluids were started on the seventh postoperative day. For the first five postoperative days there were fairly large amounts of gastric drainage (495 to 2,470 ml.). The temperature ranged from 37° to 38.3° C.

CASE 11.—V. P., a 37-year-old Negro woman, was admitted with a one-week history of right lower quadrant pain, becoming very severe one hour before admission, and three days of moderate diarrhea. Twelve hours after admission the patient was taken to surgery, where a

*Amigen (containing 30 meq. of sodium, 19 meq. of potassium, 21 meq. of chloride, and 6.11 Gm. of nitrogen per liter) was kindly furnished by Mead Johnson & Company, Evansville, Indiana.

right tubo-ovarian abscess and pelvic peritonitis were found. Right salpingo-oophorectomy and appendectomy were performed. Spinal anesthesia was employed. The patient received 1,000 ml. of 5 per cent dextrose in normal saline solution and 1,000 ml. of 5 per cent dextrose in water from the time of admission (3:30 A.M.) until 6:30 A.M. On the day of operation 1,000 ml. of whole blood, 2,000 ml. of 10 per cent fructose, 650 ml. of normal saline solution, and 200 ml. of 5 per cent dextrose in distilled water were given. For the first seven postoperative days the patient was maintained on daily intravenous infusions of 2,875 ml. of 10 per cent fructose. Oral feedings were started on the seventh postoperative day. The temperature was 39.4° C. on the day of operation and thereafter ranged from 37° to 38° C.

CASE 12.—C. S., a 62-year-old white man, was admitted with a three-hour history of abdominal and shoulder pain. The only other gastrointestinal symptoms were a one-week history of anorexia prior to admission. A roentgenogram revealed free air in the peritoneal cavity, and five hours after admission a perforated gastric ulcer was plicated. On the day of operation the patient received 2,200 ml. of 5 per cent dextrose in distilled water, 700 ml. of 5 per cent dextrose in normal saline solution, and 400 ml. of whole blood. For the next five days he was maintained on intravenous infusions consisting of 2,000 ml. of a balanced electrolyte solution,* 500 ml. of 5 per cent dextrose in water, and 200 ml. of 50 per cent dextrose in water. Oral feeding was started on the sixth day, at which time he also received 1,000 ml. of a balanced electrolyte solution and 100 ml. of 50 per cent dextrose in distilled water. The temperature ranged between 37° and 39.4° C.

CASE 13.—A. K., a 56-year-old white man with severe rheumatoid arthritis, was admitted with a five-hour history of severe abdominal pain. He had considerable weight loss during the preceding several months. A roentgenogram revealed free air under the diaphragm. Six hours after admission a large perforated gastric ulcer was biopsied and plicated. Pathologic report on the biopsy was poorly differentiated adenocarcinoma. On the day of operation the patient received 500 ml. of whole blood and 3,000 ml. of 5 per cent dextrose in distilled water. For the next three days he was maintained on intravenous infusions consisting of Travamin and 10 per cent invert sugar. The following two days he received intravenous infusions of 5 per cent dextrose in distilled water. Oral intake was started on the sixth postoperative day. The postoperative course was complicated by a two-week period of fever fluctuating between 38° and 39.5° C. The patient refused any surgical therapy for the gastric carcinoma.

CASE 14.—G. W., a 52-year-old white woman, was admitted with a six-hour history of severe lower abdominal pain most marked in the left lower quadrant, fever, and leukocytosis. Diagnosis of sigmoid diverticulosis had been made by barium enema on a previous admission. The working diagnosis was diverticulitis with perforation and peritonitis. Treatment consisted of gastrointestinal suction, antibiotics, and daily administration of 200 ml. of 5 per cent plasma hydrolysate in 5 per cent dextrose and 1,000 ml. of 10 per cent dextrose in water for seven days. The temperature subsided to normal on the second hospital day, and she was discharged improved on the eighteenth hospital day. She was subsequently readmitted for resection of the sigmoid colon for recurrent diverticulitis. Metabolic studies which were carried out on this second admission have been previously reported.[5]

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DISCUSSION

DR. JAMES DANIEL HARDY (Memphis, Tenn.).—I have only two comments: First, I suppose I should flick off any isotopes this morning, in view of Dr. Dunphy's address last evening! Second, we studied a patient who had been on intravenous fluid therapy without potassium intake for five days. Over the next four days he was able to conserve potassium by diminishing the renal excretion, although an obligatory excretion of 12 meq. continued to be lost daily. Nevertheless, there is a renal saving of potassium.

The second point comes to mind from something which was mentioned yesterday in regard to the relatively large amounts of potassium which were being given. We recently had a patient with a wet right colostomy to whom we had been giving 12 Gm. of potassium per day without obvious effect. We then gave this patient 24 Gm. or about 330 meq. as a 1.2 per cent solution of potassium chloride intravenously in twenty-four hours, with serial blood chemistry and electrocardiograms. She became fully oriented and stopped picking at the bedclothes for the first time in a week, and the urinary output, previously about 500 ml. per day, increased to 3,000 ml. on each of the subsequent two days.

DR. HENRY THOMAS RANDALL (New York, N. Y.).—I am always intrigued by metabolic balance studies which are well done, as is this one that Dr. Krieger presented here this morning.

I was particularly interested in his reiteration of the concept of a third fluid space. I think it is a little hard sometimes to realize that you can have fluid, pooled fluid, which is completely unavailable to the body and still inside it. We will all recognize it if we think about it in a patient who has an ileus, and who on x-ray of the abdomen shows fluid levels in loops of distended bowel. It is prefectly obvious that that fluid is still inside the patient technically but still is of no use to him because he is unable to absorb it.

The burn is a situation where it is a bit more obvious that the fluid is trapped somewhere and the patient becomes dehydrated into himself. This paper on peritonitis shows

beautifully what we have always assumed is the case and that is that peritonitis, if it is an acute diffuse peritonitis, is the equivalent of a 20 to 30 per cent second to third degree burn, and it requires similar treatment. The other part of the problem is the fact, as Dr. Krieger said, that when these situations begin to resolve, the patient in effect gets a large infusion from within his own body. I think probably more mistakes are made at that point than any other, because when the area of third space fluid accumulation begins to reabsorb, one must make a radical change in the fluid therapy. The supply of water and of extracellular electrolytes which suddenly becomes available can, in an older patient, result in an overload of the circulation and of the extracellular fluid unless we are aware of the fact that at this point one must temporarily greatly reduce or stop electrolyte administration, with the possible exception of potassium, and cut way down on fluid intake.

I think this is well illustrated by Dr. Krieger's cases.

DR. FRANCIS D. MOORE (Boston, Mass.).—I do not think we should prolong this discussion at all because it relates to matters of science and possibly superscience and, after all, Dr. Dunphy is tired and worn out and red-eyed after his really wonderful efforts of last night. Dr. Krieger and Dr. Abbott gave me an opportunity to read their paper, which I have done and which has given me a little time to think about it. I enjoyed it very, very much. In the paper they raise a point which Dr. Krieger did not have time to mention this morning as to how much of the changes are due to the infection and how much due to the trauma. Speaking of trauma, we have made one or two recent studies on this subject in its relation to infection.

[Slide.] Passing along from one form of trauma to another, this is a study of a patient with appendicitis without peritonitis, and these are the changes in metabolism. I would describe them as negligible and very difficult to differentiate from starvation. There is not much change in the urinary 17-ketosteroids, but the 17-hydroxycorticoids in the urine show a definite rise even with this minor trauma.

[Slide.] This patient gave us a chance to study the two quite separately. He had acute appendicitis and perforation and fecal peritonitis with appendectomy here and secondary wound closure here. Note the large nitrogen excretion—this child weighs only about 30 kilograms, which corresponds to about 20 Gm. a day in normal adults. There is not much change in 17-ketosteroids, but tremendous increase in 17-hydroxycorticoids in the urine. Then he started to "save" nitrogen, but he is not really eating yet. He then formed a secondary pelvic abcess localization, and it was interesting that the metabolic effect of this secondary inflammation of the peritoneal cavity was just like a new trauma. His nitrogen excretion went up again. He lost weight a little bit more rapidly; the ketosteroids stayed down with no change, as before, but the 17-hydroxycorticoids showed a very definite endocrine response to this relocalized infection, which to us is of interest in demonstrating the metabolic effects of the infection itself.

DR. KRIEGER (Closing).—I wish to thank the discussers for their very important remarks and say that we also have had the opportunity to study a patient who developed peritonitis following a right colectomy and noted changes similar to those described by Dr. Moore. I wish to re-emphasize the fact that the magnitude of these changes which occur in peritonitis may be much greater than the magnitude of those which are noted as a result of gastrointestinal drainage.

CHANGES IN EXTRACELLULAR WATER AND ELECTROLYTES AND THE RENAL COMPENSATIONS IN CHRONIC ALKALOSIS, AS COMPARED TO THOSE OCCURRING IN ACUTE ALKALOSIS*

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THE plasma electrolyte structure and clinical symptomatology in chronic alkalosis resulting from potassium deprivation and in acute alkalosis as produced by exogenous alkali administration may be identical. In spite of the comparative chemical picture, however, the mechanisms whereby each abnormality develops, the physiologic adjustments, and the therapeutic alleviation in the two situations are quite dissimilar. The respiratory, renal, and plasma compensations which occur following exogenous alkali invasion have been extensively defined.[14, 15]

Although the situation of hypokalemic alkalosis is a well-defined clinical entity, the physiologic alterations which contribute to this electrolyte abnormality and the attendant clinical symptomatology have remained obscure. It has been well documented that alkalosis develops in a variety of situations in which potassium deprivation or excessive losses of potassium is the common denominator.[1, 4, 6, 17, 18, 25] Such clinical conditions are legion, and include hyperadrenocorticism, postsurgical conditions with inadequate potassium intake or excessive loss, and situations where gastrointestinal losses are excessive. Concomitant with the existence of the hypokalemic alkalosis, there may be a plasma hypochloremia, frank clinical edema, depressed renal function, and the paradoxical excretion of an acid urine.[2, 3, 17-19, 27] Attempts at therapeutic alleviation of this syndrome with ammonium or sodium chloride have been reported to be ineffective.[2, 5, 17, 19] Because of the reported discrepancies between acute alkalosis and the alkalosis of potassium deprivation, it would appear that the alterations in body water and electrolytes and renal excretory mechanisms in the two situations might profitably be studied, utilizing each patient as his own control. Accordingly, the studies herein described were undertaken in situations of acute and chronic alkalosis: (1) to define the alterations between the extracellular and intracellular fluid and electrolytes occurring in the two situations, (2) to inquire into the mechanisms whereby the body buffers an alkali invasion, and (3) to measure the renal compensations implicated in the production or amelioration of alkalosis. The

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results of these studies indicate that there is a compensatory increase in the extracellular volume of water, as well as an absolute increase in the amount of extracellular chloride, bicarbonate, and sodium in both acute and chronic alkalosis! Although a decrease in extracellular potassium was found to exist in hypokalemic alkalosis, the change was insignificant in comparison to the magnitude lost from intracellular sources. In addition, it was noted that the renal compensations in acute alkalosis are effective in normal patients, whereas the renal excretory mechanisms in hypokalemic alkalosis are not only ineffective but actually contribute to the production of the alkalosis.

METHODS

In all, twenty experiments were performed on a total of nine patients; metabolic balance studies were carried out on six of these patients. The experiments were designed to study the alterations in extracellular fluid and electrolytes, as well as the renal compensations, under the following conditions: (1) in normal controls, (2) in acute alkalosis, as produced by the infusion of sodium lactate or bicarbonate, and (3) in chronic alkalosis, which occurred at intervals varying from five to nineteen days during the recuperative period of surgical patients maintained on potassium-free fluids. The alterations which occurred in acute and chronic alkalosis were then compared in the same patient. That moiety of the extracellular compartment into which inulin distributed was measured as an index of change in the extracellular water.* The volume of distribution of inulin in the control period and the changes in this volume of distribution were measured, utilizing a constant infusion technique. Following an adequate equilibration period, the inulin space was calculated according to the formula $\frac{\text{Inulin infused} - \text{Inulin excreted}}{\text{Plasma concentration}}$.[7, 24] Renal clearance of inulin was measured concomitantly and served as a measure of glomerular filtration rate, and renal plasma flow was measured utilizing the clearance of para-aminohippurate.[26] Total milliequivalents of sodium, potassium, chloride, and bicarbonate in the extracellular water were calculated as the product of the extracellular water concentration of these electrolytes and the inulin space.† The shifts of electrolytes into or from the extracellular compartment could then be estimated from a comparison of the measurable values obtained in the control and the alkalotic period, with allowance for that amount of electrolyte given, retained, or excreted in this interval.

During the development of chronic alkalosis, metabolic balance studies were carried out to determine the sodium, potassium, and chloride balance. These studies included measurement of all intake and of fecal, drainage, and urinary losses.‡ In both acute and chronic alkalosis, the excretion of bicarbonate and urinary pH was measured concomitantly with measurements of renal plasma flow and glomerular filtration rate as an index of renal tubular function.

The chemical analysis of sodium, phosphate, potassium, chloride, bicarbonate, pH, inulin, para-aminohippurate, and plasma water was carried out according to suitable methods, as described in previous communications.[19, 21] (In all the patients studied on a metabolic regime, the aim was to study the clinical situation most frequently encountered; for this reason, the induced alkalosis was only moderately severe.)

*It is generally recognized that inulin may not accurately measure the entire extracellular compartment nor does it penetrate the gastrointestinal tract.[12] Because of the vagaries of inulin distribution, it is utilized here only as an index of that extracellular fluid into which inulin is equally distributed.

†A Donnan factor of 1.05 for chloride and bicarbonate and 0.95 for sodium and potassium was used in these calculations.

‡In these studies the attendant difficulties in measuring insensible loss of electrolytes were prohibitive. For this reason, such occult losses were ignored in the over-all metabolic calculations.

RESULTS

Acute Alkalosis.—Table I shows the typical alterations which occurred in patients during acute and chronic alkalosis. As indicated here, both situations are characterized by a fall in plasma potassium and chloride and an elevation of bicarbonate-bound base and pH. Concomitant with the alterations in electrolyte structure, there was an increase in that component of extracellular fluid which is measured by inulin, amounting to 2 L. or more. Although there is an apparent drop in the plasma concentration of chloride in acute alkalosis, this did not accurately reflect the total number of milliequivalents in the inulin space (Table II). Calculation of the total milliequivalents of chloride in the inulin compartment, as a product of the plasma water concentration and the inulin space, indicates that there was, in fact, a net increase in the total milliequivalents of chloride. Similar calculations for sodium, potassium, and bicarbonate indicate an increase in the total milliequivalents of sodium and bicarbonate, which was also of greater magnitude than that reflected by plasma analysis. From such a calculation of the total amount of sodium, chloride, or bicarbonate in the inulin space, and subtracting from this figure the amount administered, it was possible to quantitate the number of milliequivalents which had shifted into the inulin space. Calculations made in this manner are also shown in Table II, and indicate that the net transfers of sodium and chloride into the extracellular inulin space in acute alkalosis are approximately equivalent. In this patient, as well as in four others, some fraction of the administered bicarbonate shifted from the inulin space during the period of study. Equivalent alterations in the inulin space and extracellular electrolytes occurred in all the patients studied in this manner. Fig. 1 summarizes these changes in four patients during acute alkalosis, and graphically illustrates the increase in the volume of distribution of inulin, as well as the increase in total milliequivalents of sodium, chloride, and bicarbonate in this extracellular compartment.

TABLE I. PATIENT H. PLASMA ELECTROLYTE CONCENTRATIONS AND INULIN SPACE ALTERATIONS: CONTROL, ACUTE, AND CHRONIC ALKALOSIS

	PLASMA							INULIN SPACE (L.)
	Na	K	Cl	$BHCO_3$	Mg	PO_4 mM/L.	pH	
	(MEQ./L)							
	Acute Alkalosis							
Control	142	4.6	105	28.4	1.37	1.4	7.4	11.4
	(Infuse 167 meq. sodium lactate)							
Alkalosis (acute)	143	3.5	100	31.7	1.00	1.3	7.48	13.9
Control	142	4.0	105	27.4	1.62	1.9	7.4	12.2
	(Potassium-free regime 6 days)							
Alkalosis (chronic)	137	3.0	97	31.2	1.27	1.2	7.49	14.4

TABLE II. PATIENT Z. CHANGE IN TOTAL EXTRACELLULAR ELECTROLYTES AND THE ESTIMATED SHIFTS OF CHLORIDE, SODIUM, AND BICARBONATE OCCURRING IN THE SITUATION OF ACUTE ANKYLOSIS

	SODIUM	CHLORIDE	POTASSIUM	BICARBONATE
	(TOTAL MILLIEQUIVALENTS IN INULIN SPACE)			
Control	1,653	1,345	53	365
Alkalosis (acute)	2,029	1,570	49	497
Gain	+376	+225	−4	+132
Given	167	0	0	167
Shifted	+209	+225	−4	− 35

Renal Compensations.—Following the administration of lactate or bicarbonate to a normal patient, the urine becomes frankly alkaline, and considerable quantities of bicarbonate-bound base are excreted. This renal response to an alkali load is shown in Fig. 2. At plasma bicarbonate concentrations greater than 27 to 29 meq. per liter, the urine becomes alkaline, and urinary

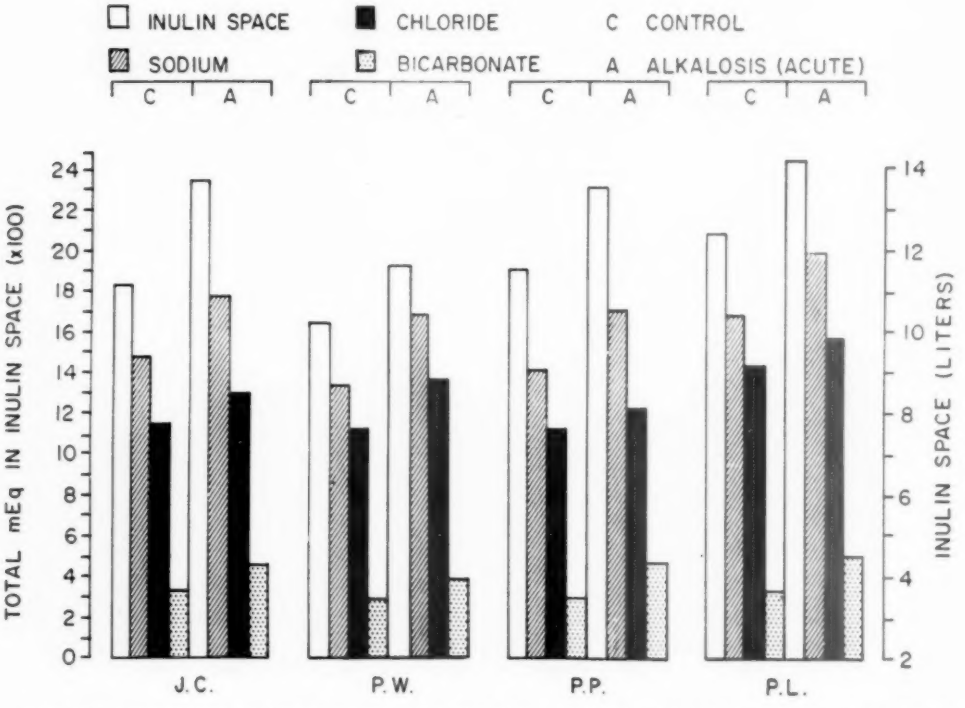

Fig. 1.—Alterations in inulin space and the total sodium, chloride, and bicarbonate in the inulin space which occurred in acute alkalosis, as produced by infusion of 1 L. of M/6 sodium lactate.

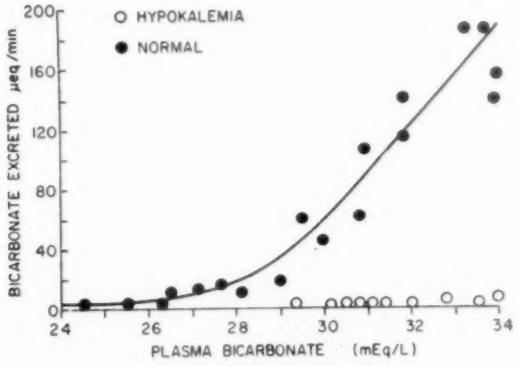

Fig. 2.—Renal excretion of bicarbonate following lactate or bicarbonate infusion in five patients (solid circles). Renal excretion of bicarbonate in hypokalemic alkalosis in nine patients (open circles).

excretion of bicarbonate rises in a linear fashion. Such a renal response to the administered bicarbonate results in correction of the plasma alkalosis within twelve to eighteen hours.

Chronic Alkalosis.—With the patients on a metabolic regime, calculations of retention or losses of electrolytes could be obtained from measurements of

the intake of sodium and chloride and the urinary, fecal, and drainage losses of electrolyte. From these calculations and from measurements of the change in the inulin space and electrolytes, it was possible to determine electrolyte and water shifts which occurred in the situation of hypokalemic alkalosis. The results and calculations of one such study are shown in Table III. The figures shown here indicate an increase in the total number of milliequivalents of sodium, chloride, and bicarbonate in the inulin space. This occurred despite the apparent loss of chloride and sodium, as reflected by a decrease in the plasma concentrations of these ions (Table I). In this patient, as well as in five others studied in this manner, there was a greater retention of sodium than chloride during the postoperative period. In all of these patients, the retained sodium could be accounted for in the inulin space; the amount of chloride in the inulin space was greater, however, than that retained. We have interpreted this increase of extracellular chloride in the absence of marked retention as a shift from some source in the body other than the space measured by inulin. Similar results in four other patients are illustrated in Fig. 3, which summarizes the magnitude of change in the volume of distribution of inulin and total extracellular chloride, bicarbonate, and sodium.

TABLE III. ALTERATIONS IN TOTAL SODIUM, CHLORIDE, BICARBONATE, AND THE CALCULATED SHIFT OF CHLORIDE WHICH OCCURS IN HYPOKALEMIC ALKALOSIS. RETENTION OR LOSSES OF ELECTROLYTES WERE CALCULATED FROM METABOLIC BALANCE DATA

	SODIUM	CHLORIDE	POTASSIUM	BICARBONATE
	(TOTAL MILLIEQUIVALENTS IN INULIN SPACE)			
Control	1,769	1,446	49	377
Alkalosis (chronic)	2,015	1,577	44	507
Change	+246	+131	–5	+130
Retained (metabolic balance)	+225	+ 34	–182	–
Shifted	+ 21	+ 77	–	–

In marked contrast to the compensations afforded by the renal tubules in acute alkalosis, the situation of hypokalemic alkalosis was characterized by the renal excretion of only trace amounts of bicarbonate-bound base. Fig. 2 demonstrates this failure of the kidneys to excrete an alkaline urine at a time when the plasma bicarbonate was markedly elevated. This finding, together with the observation that sodium was retained in excess of chloride, we have presumed to be evidence that the excess sodium is retained as bicarbonate-bound base.

A decrease in glomerular filtration rate and renal plasma flow of roughly 20 per cent was observed in one patient in whom hypokalemic alkalosis existed. Such decreases in renal functional measurements did not, however, compromise the renal excretory mechanisms for titratable acid, ammonium, or phosphate.

Electrocardiographic Alterations.—Electrocardiographic alterations were observed in four of the patients studied, which were compatible with hypokalemia and/or alkalosis.[1, 4, 6, 18, 25] In no patient was there any correlation of the electrocardiographic changes with the degree of plasma hypokalemia.

Potassium.—Worthy of note was the finding in these patients that neither the plasma potassium level nor the total potassium in the inulin space reflected anything but a microscopic portion of the changes occurring in total body potassium, as measured from balance studies. This observation is illustrated in Fig. 4. In these patients the total potassium in the inulin space showed a decrease ranging between 2 and 10 meq., and the plasma potassium level dropped an average of 1 to 1.5 meq. per liter. This decrease in plasma and

extracellular potassium occurred in the face of total potassium losses of 180 to 280 meq. With the progression of the hypokalemic period, the renal excretion of potassium diminished markedly. Potassium concentrations as low as 2 to 6 meq. per liter, with total excretions of 6 to 18 meq. per day, were observed in these patients toward the termination of the hypokalemic interval.

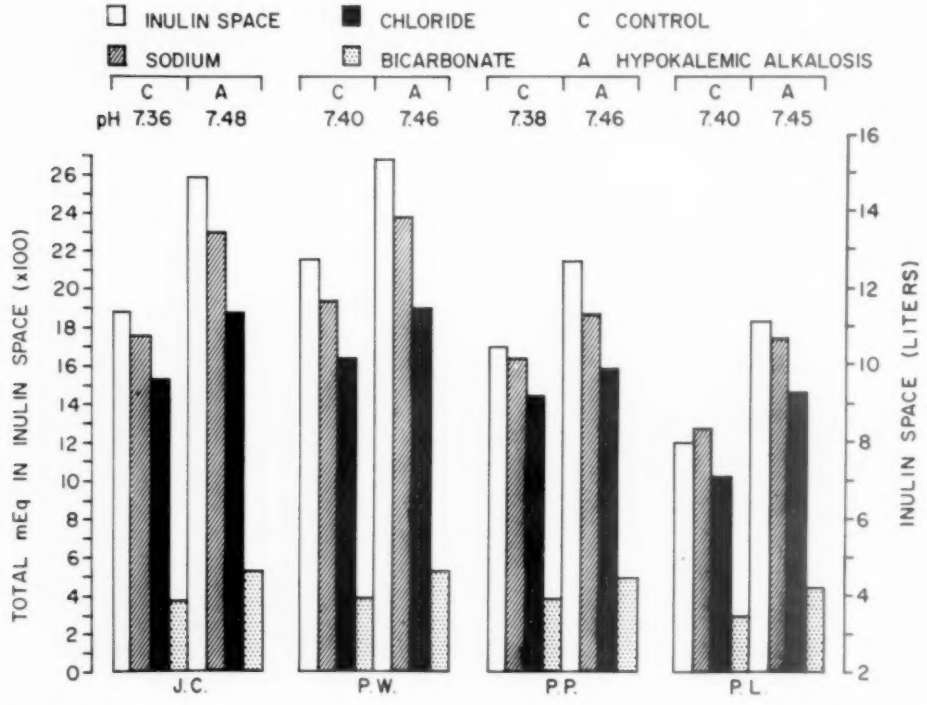

Fig. 3.—Changes in inulin space and total milliequivalents of sodium, chloride, and bicarbonate in hypokalemic alkalosis.

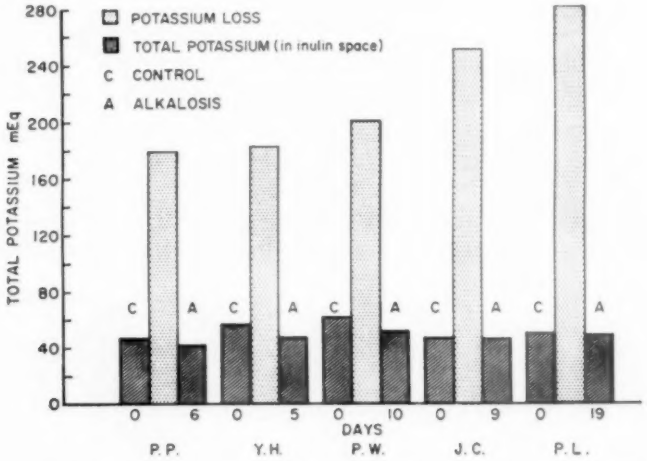

Fig. 4.—Total extracellular potassium in control and hypokalemic states in comparison to the total body losses of potassium (as measured from metabolic balance data).

Comparison of Extracellular Fluid Changes Utilizing Chloride Balance Data and Direct Measurements With Inulin.—In view of the finding illustrated previously and the evidence that chloride may shift into the inulin space in situa-

tions of alkalosis, it seemed appropriate to make a comparison between the changes in extracellular fluid and electrolytes. Table IV shows this comparison, as calculated from chloride balance data and the inulin space. Such a comparison appeared to be especially pertinent, since many of the conclusions and data which have been accepted as existing in alkalosis have been based on the measurements calculated from the chloride balance data. These calculations were made according to the method of Gamble,[9] and depend upon the assumption that the chloride ion is exclusively extracellular. As shown in Table IV, there is considerable discrepancy between the extracellular space and the total electrolytes in this space, as measured directly by inulin and calculated from chloride balance data. In the latter situation, all the measured components are considerably smaller.

TABLE IV. PATIENT W. COMPARISON OF THE CALCULATED VALUES FOR EXTRACELLULAR WATER, CHLORIDE, POTASSIUM, SODIUM, AND BICARBONATE, CALCULATED FROM CHLORIDE BALANCE DATA AND FROM THE VOLUME OF DISTRIBUTION OF INULIN

CHRONIC ALKALOSIS	CALCULATED FROM CHLORIDE BALANCE DATA	CALCULATED FROM VOLUME OF DISTRIBUTION OF INULIN
Extracellular water (L.)	15	16.4
Chloride (meq. in E.C.W.)	1,755	1,910
Potassium (meq. in E.C.W.)	43.4	47.5
Sodium (meq. in E.C.W.)	2,200	2,400
Bicarbonate (meq. in E.C.W.)	470	517

E. C. W.: Extracellular water.

DISCUSSION

From these data and calculations, it is apparent that the physiologic adjustments and mechanisms in acute and chronic alkalosis are similar only in respect to the alterations in electrolytes and extracellular fluid volumes. Following the administration of alkali, there occurred an increase in that volume of extracellular fluid measured by inulin and a concomitant increase in sodium, chloride, and bicarbonate, with little change in potassium. That the magnitude of these changes was not apparent from measurements of the plasma concentrations per se presumably results from the extracellular dilution which occurs in alkalosis. Of major importance was the finding that there was an increase in the total amount of chloride in the inulin compartment in both acute and chronic alkalosis, which was not accounted for by administered or retained chloride. On this basis, the presumption is inherent that a shift of this ion occurred from some source other than the inulin compartment. In the situation of acute alkalosis, there was an increase in sodium which was roughly parallel to the rise in chloride.[10] In contrast, chloride alone was found to have shifted into the inulin compartment in chronic alkalosis, whereas the increase in sodium could be entirely accounted for by retention. Although this shift of chloride could occur from bone, collagenous tissue, or conceivably from other intracellular sources,[15, 16, 28] assumptions as to this source are untenable in the absence of detailed analysis of these structures. Although our findings are somewhat in variance with experimental work of Pitts,[16] who found only shifts of chloride in acute alkalosis, our experimental setup differs from theirs in that these investigators studied the effects of bicarbonate infusion in anes-

thetized, nephrectomized dogs. Under these conditions, the effect of anesthesia and the complications afforded by acute surgical trauma and nephrectomy do not present a situation completely analogous to the conditions under which our experiments were carried out. In either case, the dilution of the extracellular compartment and the shifts of chloride consequent to alkali invasion would tend to obviate or lessen severe alterations in plasma pH which might otherwise occur following an alkaline load.

In addition to the compensations afforded by shifts of fluid and electrolytes to minimize pH changes, there are also compensatory renal mechanisms for the excretion of excess alkali in situations of acute alkali loading.[14, 15, 19] Since the renal tubules of normal man reabsorb some 2.7 to 2.9 meq. of base-bound bicarbonate per 100 c.c. of plasma filtered, all bicarbonate in excess of this amount, when presented to the renal tubules, is excreted. In this manner the renal tubular mechanisms compensate an acute invasion of alkali within ten to eighteen hours following its administration. Such was found to be the case in the patients studied here.

In the clinical circumstance of hypokalemic alkalosis, the renal excretory mechanisms for base-bound bicarbonate fail, and the urine remains acid and contains sparse amounts of bicarbonate. Not only do the renal mechanisms fail to alleviate this situation but, from evidence shown previously and presented elsewhere, renal alterations in the reabsorption of bicarbonate may be indicted in the production of the alkalosis seen in hypokalemia.[19, 22] Presumptive evidence indicates that tissue potassium depletion results in a drop in intracellular pH; such alterations in intracellular composition in renal tubular cells could potentiate the renal tubular reabsorption of base-bound bicarbonate, which then exceeds that normally described for man. With the continued retention of bicarbonate, plasma alkalosis could develop concomitant with the excretion of an acid urine. Impetus is given to this concept by the observation that potassium chloride administration is followed by an increased excretion of bicarbonate[11, 19] resulting from a decrease in the amount of bicarbonate reabsorbed by the renal tubules. Further, this alteration in reabsorption of bicarbonate may be effected either in a normal or hypokalemic patient. Following administration of potassium chloride, alterations in bicarbonate reabsorption occur concomitant with a decrease in plasma bicarbonate and pH.[19] Although the studies reported here and elsewhere emphasize that the kidney is implicated in the production of hypokalemic alkalosis and its amelioration when potassium is given, they do not preclude tissue electrolyte alterations following the withdrawal or administration of potassium salts. Nor does an acute drop in plasma potassium specifically influence bicarbonate reabsorption; only with losses of considerable magnitude from intracellular stores is reabsorption increased.[19]

Because the clinical picture of hypokalemic alkalosis may be evident in hyperadrenocorticism, and because of the salt-retaining effects of the adrenal steroids, the adrenal cortex has been implicated in the production of this syndrome.[13] However, this need not be the case, since the administration of corti-

sone or desoxycorticosterone has been shown to have no acute effect on bicarbonate excretion or reabsorption.[19] It is more likely that the alkalosis seen in situations associated with excess adrenal steroid is secondary to the potassium depletion which may occur following excessive steroid administration or production. The finding that potassium salts correct the hypokalemic alkalosis seen in these situations lends credence to the latter assumption.[11, 23]

Of considerable interest was the finding that neither the plasma potassium level nor the total milliequivalents in the extracellular inulin space reflected the total body potassium depletion. In all patients studied, the intracellular potassium was depleted, while a minimal, absolute loss of this electrolyte occurred from the extracellular compartment and, in many instances, plasma levels remained within low normal range. Such discrepancies in the total loss of potassium and the minimal changes in the extracellular level of this ion serve to indicate that extracellular potassium is, at best, a poor reflection of changes occurring in total body potassium. A more precise index of potassium depletion appeared to be a consistent elevation in the plasma level of base-bound bicarbonate. For this reason, it would appear that plasma bicarbonate concentrations might serve as an important adjunct in the clinical evaluation of suspected potassium depletion.

In four of the patients studied, electrocardiographic alterations consistent with hypokalemia and/or alkalosis were noted. In none of the cases was there any correlation with the plasma potassium level. From these observations and from those reported elsewhere, impetus is given to the theory that the symptomatology and electrocardiographic findings in hypokalemia are the result of the extracellular-intracellular concentration gradients of potassium and perhaps bicarbonate and pH as well, with consequential changes in cellular membrane potentials.[20]

Although a drop in the plasma concentration of chloride occurred in the patients studied, the decrease was an apparent one only. Calculation of the total chloride in the inulin space showed that the actual amount of chloride was, in fact, increased. This increase in the total chloride does not substantiate the premise that the plasma alkalosis associated with hypokalemia is the result of selective loss of chloride.* The finding that elevations in total chloride in the extracellular inulin space resulted in part from shifts of this ion assumes considerable importance in the evaluation of changes in extracellular water and electrolytes which are derived from calculations based upon chloride balance techniques.[7-9] Such studies are founded upon the assumption that chloride is an obligatory extracellular ion and that changes in external balance and concentration can be used as a measure of changes in extracellular fluid. Comparison of values for extracellular fluid and total electrolytes by the method of chloride balance measurements, as compared to measurements utilizing the volume of distribution of inulin, shows considerable variance

*No attempt is made in these studies to delineate the acute alkalosis resulting from gastric losses. In this situation, there is presumed to be a selective loss of chloride from body fluids resulting in an excess of bicarbonate-bound base. Although a selective loss of chloride would result in a plasma chemical picture of hypochloremia, hypokalemia, and alkalosis, the pathogenesis and treatment would obviously differ from the acute and chronic alkalosis as described in these studies.

(Table IV). Such a discrepancy may well result from the erroneous assumption that chloride is an obligatory, extracellular ion, and from the failure to account for the shifts of chloride into the extracellular space from some source other than that measured by inulin.[28] Cognizance of the fallacies inherent in measuring the inulin space does not permit the conclusion, however, that the inulin space is a completely valid measure of the entire extracellular compartment; hence, one can only make the reservation that the inulin and chloride space and the electrolytes distributed in the space are not equal under the conditions imposed by this study.

SUMMARY AND CONCLUSIONS

1. The physiologic alterations occurring in acute alkalosis and hypokalemic alkalosis have been studied and compared in adult human subjects.

2. The volume of extracellular fluid, as measured by inulin, and the absolute amount of chloride, sodium, and bicarbonate in this space increased in both acute and chronic alkalosis; the magnitude of this electrolyte change was not reflected by plasma concentration alone.

3. Evidence has been presented to show that shifts of chloride into the inulin space occur in hypokalemic alkalosis, whereas both sodium and chloride shift in the situation of acute alkalosis. It has been postulated that the shift of water and electrolytes is a physiologic adjustment of the body to minimize alterations in pH.

4. The plasma level of potassium and the total milliequivalents in the inulin space are minimally altered in comparison to the total body losses of potassium, as measured by metabolic balance studies during the development of hypokalemic alkalosis.

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SPLENECTOMY, CORTISONE, AND CORTICOTROPHIN (ACTH) IN THE TREATMENT OF CERTAIN BLOOD DYSCRASIAS

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THE therapeutic value of splenectomy in certain blood dyscrasias is well established and has long since been thoroughly documented.[1] No one questions, for example, its efficacy in controlling congenital hemolytic anemia, primary splenic neutropenia, or primary splenic pancytopenia. Likewise, in idiopathic thrombocytopenic purpura, most authors[2, 3] are agreed that removal of the spleen remains as the most effective form of therapy known today for the majority of the cases, although the results are by no means as consistent as in those conditions just cited. In the acquired hemolytic anemias, symptomatic thrombocytopenic purpuras, and certain additional dyscrasias which may be loosely categorized as examples of secondary hypersplenism, the results of splenectomy are variable and unpredictable, and the operation is usually undertaken only when other therapeutic measures have failed.

It was quite natural, therefore, when cortisone and ACTH appeared on the therapeutic horizon in 1949, that these agents were given a most extensive trial in those blood dyscrasias either in which splenectomy had already been tried and proved a failure or in which the results of the operation were unpredictable or poor. The fact that the use of the hormones under these circumstances was *not* uniformly successful, necessitating a further trial of splenectomy if this measure had not already been undertaken, has provided the material for this paper.

In this connection, it seems pertinent to recall that, initially, high hopes for the therapeutic effectiveness of cortisone and ACTH in many special fields were held throughout the medical profession at large. In the light of present-day knowledge, and as the data about to be presented will substantiate, these hopes were better justified in the field of hematology than in many others.[4] It is now well known, for example, that these hormones can profoundly affect allergic and immunologic responses, as well as capillary fragility[4, 5]—factors of fundamental significance in certain of the more important disorders of the spleen.

A review of the literature disclosed forty-one pertinent articles[5-49] or case reports on the subject of the use of cortisone and ACTH in thrombocytopenic purpura and hemolytic anemia. The authors were, for the most part, primarily interested in what the hormones by themselves may accomplish. The role of splenectomy in conjunction with their employment was discussed but not, in general, emphasized. Many observers commented on the usefulness of cortisone and ACTH in preparing patients with purpura or hemolytic anemia for surgery or in tiding individuals over recurrences when splenectomy had failed. Data relevant to the results of the combined use of cortisone, ACTH, and surgery, however, were generally scant or incomplete.

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Table I contains a compilation of the experience of various authors with the use of cortisone and/or ACTH in the treatment of thrombocytopenic purpura. In this table, the results of cortisone/ACTH treatment are classified as "Excellent," "Good," and "Failure": "Excellent" indicates a complete clinical as well as hematologic remission produced by the drugs and maintained after their withdrawal for as long as followed; "Good" signifies a complete clinical as well as hematologic remission, which was maintained only so long as the cortisone and/or ACTH was administered, a relapse occurring after their withdrawal; "Failure" includes not only those cases in which the drugs produced no discernible effect whatever, but also those instances in which clinical improvement without hematologic betterment occurred. This latter group, in which the bleeding tendency was controlled without a concomitant platelet rise, could not be clearly separated from the complete failures in the case reports in the literature.

TABLE I. RESULTS OBTAINED WITH CORTISONE/ACTH IN THE TREATMENT OF THROMBOCYTOPENIC PURPURA (REVIEW OF PREVIOUSLY REPORTED SERIES)

		CORTISONE/ACTH ALONE OR PRIOR TO SPLENECTOMY				CORTISONE/ACTH SUBSEQUENT TO SPLENECTOMY			
AUTHORS	TOTAL CASES	NUMBER OF CASES	EXCELLENT	GOOD	FAILURE*	NUMBER OF CASES	EXCELLENT	GOOD	FAILURE*
Robson, 1950[5]	2	2	1	1	0	0	—	—	—
Single cases[6-9, 18, 20]	6	4	2	2	0	2	1	1	0
Jacobson, 1952[10]	3	1	0	1	0	2	0	2	0
Faloon, 1952[11]	2	1	1	0	0	1	0	1	0
Davidson, 1952[12]	10	8	3	2	3	2	0	1	1
Stefanini, 1952[13]	8	5	0	3	2	3	2	0	1
Meyers, 1952[14]	17	16	5	6	5	1	0	1	0
Wilson, 1952[15]	12	11	3	1	7	1	0	1	0
Havermark, 1953[16]	3	3	0	3	0	0	—	—	—
Harrington, 1953[17]	18	14	2	2	10	4	2	0	2
Eisen, 1953[19]	3	3	1	1	1	0	—	—	—
Greene, 1953[21]	7	7	0	2	5	0	—	—	—
Adamson, 1953[22]	3	3	0	1	2	0	—	—	—
Hewlett, 1953[23]	7	7	0	2	5	0	—	—	—
Total	101	85	18 (21%)	27 (32%)	40 (47%)	16	5	7	4

*Including cases in which there was temporary symptomatic improvement without a rise in platelet count.

Table I is divided into two main categories, those receiving hormone therapy alone or prior to splenectomy, and those having this therapy subsequent to splenectomy. It may be seen that 21 per cent of the unoperated cases obtained an excellent result, 32 per cent good, and 47 per cent failure. When the

splenectomy failures are included, the percentage results achieved are approximately the same.

Table II is composed of a review of the experience of various authors with the use of cortisone and/or ACTH in the treatment of acquired hemolytic anemia. Its form is identical with that of Table I. Thirty-two per cent of this group of cases obtained a complete and prolonged remission without splenectomy, 52 per cent were adequately controlled as long as hormones were given, and 16 per cent were failures. When nine splenectomy failures in patients who received hormones are included, no percentage improvement is noted.

TABLE II. RESULTS OBTAINED WITH CORTISONE/ACTH IN THE TREATMENT OF ACQUIRED HEMOLYTIC ANEMIAS (REVIEW OF PREVIOUSLY REPORTED SERIES)

		CORTISONE/ACTH ALONE OR PRIOR TO SPLENECTOMY				CORTISONE/ACTH SUBSEQUENT TO SPLENECTOMY			
AUTHORS	TOTAL CASES	NUMBER OF CASES	EXCELLENT	GOOD	FAILURE	NUMBER OF CASES	EXCELLENT	GOOD	FAILURE
Wintrobe, 1952[8]	3	2	0	2	0	1	0	1	0
Davidson, 1952[12A]	5	4	1	2	1	1	0	0	1
British Medical Research Council, 1952[12B]	11	11	3	5	3	0	—	—	—
Bethell, 1952[14]	7	7	1	5	1	0	—	—	—
Gardner, 1952[25]	6	5	0	5	0	1	1	0	0
Dameshek, 1952[26]	22	22	14	6	2	0	—	—	—
Young, 1952[28]	2	2	0	2	0	0	—	—	—
Stickney, 1952[34]	11	11	1	5	5	0	—	—	—
Sacks, 1952[35]	11	11	5	6	0	0	—	—	—
Davis, 1952[36]	4	3	0	2	1	1	0	1	0
Hansen, 1952[37]	4	4	2	1	1	0	—	—	—
Single cases[8, 24, 27, 30-33, 37-39]	10	5	1	4	0	5	2	2	1
Total	96	87	28 (32%)	45 (52%)	14 (16%)	9	3	4	2

PRESBYTERIAN HOSPITAL SERIES

From Sept. 1, 1949, to Jan. 1, 1954, 43 patients with various types of blood dyscrasias (exclusive of those associated with portal hypertension) underwent splenectomy on the adult surgical service of the Presbyterian Hospital. Twenty-two of the 43 received cortisone and/or ACTH in addition to the operation either before or after surgery. Three patients with thrombocytopenic purpura who had splenectomy performed prior to 1949 and were failures are included in the series receiving hormones, making the total 25. Twenty-one patients had splenectomy alone. The three principal types of blood disorders for which treatment was undertaken are shown in Table III. Of the 22 cases of thrombocytopenic

purpura, 14 patients were treated with splenectomy and hormones and 8 with splenectomy alone. Eighteen of the total group of 22 were classical examples of idiopathic thrombocytopenic purpura. The remaining 4 were patients with thrombocytopenic purpura secondary to lupus erythematosus, whose true diagnosis was suspected but not proved prior to operation and whose purpura was severe enough to warrant a trial of splenectomy. Three of these 4 patients received the combined form of treatment. Two of the 4 (1 treated with hormones and 1 without) have died of disseminated lupus to date.

TABLE III. DISTRIBUTION OF CASES IN PRESBYTERIAN HOSPITAL SERIES

	TREATED WITH SPLENECTOMY, CORTISONE/ACTH	TREATED WITH SPLENECTOMY ALONE	TOTAL
Thrombocytopenic purpuras	14	8	22
Hemolytic anemias	6	6	12
Miscellaneous hypersplenism	5	7	12
Total	25	21	46

THROMBOCYTOPENIC PURPURA

Table IV shows the results of treatment with hormones and splenectomy. In classifying the response to drug therapy, the term "satisfactory remission" signifies a complete cessation of the bleeding diathesis with a concomitant rise of the platelets to normal levels, irrespective of whether the remission was maintained after drug withdrawal. The designation "symptomatic improvement" is reserved for those cases in which the hemorrhagic tendency was controlled by the hormones, but no significant platelet rise was produced. This category is emphasized because these patients may have splenectomy as an elective rather than as an emergency procedure.

TABLE IV. THROMBOCYTOPENIC PURPURAS: RESULTS OF TREATMENT WITH CORTISONE/ACTH AND SPLENECTOMY

	NUMBER OF CASES	CORTISONE/ACTH RESPONSE			SPLENECTOMY RESPONSE		
		SATISFACTORY REMISSION	SYMPTOMATIC IMPROVEMENT	FAILURE	EXCELLENT	DOUBTFUL	FAILURE
Cortisone/ACTH preoperatively	10*	3	3	4	7	2	1
Cortisone/ACTH postoperatively	4	2	2	0	0	1	3
Total	14	5	5	4	7	3	4
Splenectomy alone	8	—	—	—	5	1	2

*Three patients received cortisone postoperatively, in addition.

Ten patients received hormone therapy preoperatively, 3 gaining a satisfactory remission, 3 symptomatic improvement, and 4 failure. Two of the 4 failures in the group treated preoperatively may have resulted from giving less than the usual amount of drugs. When 4 patients are considered in addition, who had hormone therapy postoperatively because of failure to respond to splenectomy alone, the summary of results obtained is 5 satisfactory remissions and 5 symptomatic improvements. Three of these 4 had a splenectomy prior to the beginning of this study.

The customary dosage schedule of hormone therapy employed in the majority of patients for all categories was as follows: Initially, the patients received 300 mg. of cortisone during the first twenty-four hours, 200 mg. during the second twenty-four hours, and 100 to 150 mg. daily thereafter for two to

three weeks. In preparing patients for operation, the dose of cortisone was gradually decreased in the five days immediately preceding surgery, substituting approximately an equivalent amount of ACTH. No cortisone was given for two to three days preoperatively, and the final dose of gradually decreasing amounts of ACTH was 25 mg. on the day of operation. In general, no hormones were given during the immediate postoperative period.

RESPONSE TO SPLENECTOMY

Of the 10 patients receiving cortisone or ACTH preoperatively, splenectomy produced a sustained remission in 7, was of doubtful value in 2, and failed in 1. Two of 3 not responding to splenectomy did not respond to preoperative hormonal treatment, but subsequent to operation entered a sustained remission induced by cortisone. The third patient, who had had an excellent response to cortisone and ACTH before operation, died three weeks postsplenectomy of disseminated lupus.

It may be seen that the results achieved in 8 patients having splenectomy alone are reasonably good. Five had an excellent response, 1 was doubtful, and 2 were failures. The patient having a doubtful response to surgery is currently receiving hormone therapy and the 2 failures have died. One of these 2 failures had an underlying lupus and achieved a remission for two and one-half years prior to death; the other, a patient with idiopathic purpura, succumbed in the immediate postoperative period. The conclusion may be drawn that those patients having a poor or otherwise inadequate response to surgery should receive hormone therapy.

HEMOLYTIC ANEMIAS

A total of 12 patients with hemolytic anemias were studied and are listed in Table V. Three patients who received hormone therapy preoperatively were failures. Two of these 3 had an excellent response following splenectomy, and the third was doubtful. This patient was given hormone therapy postoperatively with sufficient resultant improvement to justify discontinuing treatment over one year ago. All 3 patients who received hormone therapy after splenectomy failure obtained an excellent response. It should be observed that 1 of these 3 received cortisone before operation with no benefit. Six patients having splenectomy alone resulted in 5 excellent responses and 1 failure, the latter patient dying two years postoperatively without having received hormone treatment. Five of the 6 patients having splenectomy with excellent response and without hormone therapy were considered to have a spherocytic anemia. Again it may be seen that hemolytic anemias failing to respond to splenectomy should have hormone therapy.

TABLE V. HEMOLYTIC ANEMIAS: RESULTS OF TREATMENT WITH CORTISONE/ACTH AND SPLENECTOMY

	NUMBER OF CASES	CORTISONE/ACTH RESPONSE		SPLENECTOMY RESPONSE		
		EXCELLENT	FAILURE	EXCELLENT	DOUBTFUL	FAILURE
Cortisone/ACTH preoperatively	3*	0	3	2	1	0
Cortisone/ACTH postoperatively	3†	3	0	0	0	3
Total	6	3	3	2	1	3
Splenectomy alone	6	—	—	5	0	1

*One received cortisone/ACTH postoperatively, in addition.
†One received cortisone/ACTH preoperatively, in addition.

MISCELLANEOUS HYPERSPLENISM

Twelve patients in this group were subjected to splenectomy, as shown in Tables VIA and VIB, 7 of whom had splenectomy alone. Four of these 7 had an excellent result, and 3 were failures.

TABLE VIA. MISCELLANEOUS HYPERSPLENISM: RESULTS OF TREATMENT WITH CORTISONE/ACTH AND SPLENECTOMY

	NUMBER OF CASES	CORTISONE/ACTH RESPONSE		SPLENECTOMY RESPONSE		
		EXCELLENT	FAILURE	EXCELLENT	DOUBTFUL	FAILURE
Cortisone/ACTH preoperatively only	2	0	2	0	1	1
Cortisone/ACTH pre- and postoperatively	3	1	2	0	1	2
Total	5	1	4	0	2	3
Splenectomy alone	7	—	—	4	0	3

TABLE VIB. MISCELLANEOUS HYPERSPLENISM: DIAGNOSIS CORRELATED WITH RESULTS OF TREATMENT

HYPERSPLENISM AND PANCYTOPENIA DUE TO:	NUMBER OF CASES	CORTISONE/ACTH RESPONSE		SPLENECTOMY RESPONSE		
		EXCELLENT	FAILURE	EXCELLENT	DOUBTFUL	FAILURE
Lymphoma or leukemia	4*	—	2	—	—	4
Cirrhosis (Laennec's)	1	—	1	—	1	—
Boeck's	1	—	1	—	—	1
Myeloid metaplasia	1	—	—	—	—	1
Gaucher's	1	—	—	1	—	—
Cause unknown	4†	1	—	3	1	—
Total	12	1	4	4	2	6

*Two treated with combined cortisone/ACTH therapy.
†One treated with combined cortisone/ACTH therapy.

Of the remaining 5 treated with hormones, 2 received the drugs preoperatively alone without benefit. Following splenectomy, 1 was doubtful and the other a failure of response. Three of the 5 received hormone therapy both before and after operation. One of the 3 had a temporary response preoperatively and a doubtful one following splenectomy. The other 2 were failures of both splenectomy and hormone therapy.

DISCUSSION

The results reported herein confirm the experience of others that cortisone and ACTH when given in adequate dosage may be important adjuvants to the surgical therapy of the thrombopenic purpuras and hemolytic anemias. As noted in Table IV, in slightly more than one-half of the purpuras requiring splenectomy, the bleeding tendency was controlled with these drugs prior to operation. When this occurs, the operation may be converted from an emergency procedure into one of election. In addition, it permits an unhurried technical performance with a minimum of blood loss.

It is important to bear in mind when discussing the results of any form of management of the thrombocytopenic purpuras that patients with this ailment are notoriously subject to spontaneous remissions and to relapses of varying degrees of severity. The fact that patients exhibiting long-term, appar-

ently successful splenectomy results may suddenly undergo a recurrence of the disease is only too well known. A typical example of this occurred in one of the "splenectomy failures" in the Presbyterian Hospital series reported herein. This patient had a splenectomy in 1932, and to all intents and purposes was well for twenty years. In 1952, a sudden recurrence of the disease developed. Following treatment with cortisone, the condition is once again in remission. The conclusion seems obvious that the longer these patients are followed, the more apparent it becomes that no completely satisfactory form of treatment for achieving permanent cure is as yet available for this condition. Since cortisone and ACTH have been used for the treatment of the purpuras for not more than five years, any apparent "permanency" of remission must be viewed with a certain amount of caution.

In acquired hemolytic anemia, the experience reported by others is one of 84 per cent excellent or good results achieved with hormone therapy alone (Table II). The surgeon is therefore concerned with the remaining 16 per cent who may require operation. Two of 3 patients in our series (Table V) who failed to respond to hormone therapy had an excellent result following splenectomy. It is probable that the preoperative use of hormones did not influence the results expected from operation in these cases. It is consequently apparent that surgery may increase the over-all excellent or good results in this type of disease. Two patients who had splenectomy alone and 1 who had surgery after previously unsuccessful hormone therapy were failures. These same patients were converted to "excellent results" when the drugs were given postoperatively. It may be that the preoperative use of hormones in the 2 patients treated by surgery alone would have obviated the need for splenectomy. We are in agreement with others in recommending that all patients with acquired hemolytic anemia should receive a trial of hormone therapy before surgery is undertaken.

Experience gained with the use of cortisone/ACTH therapy in miscellaneous hypersplenism, cited in Tables VIA and VIB, is meager and not encouraging. While the results are as expected, it is planned to employ the drugs in selected cases on a continued trial basis. Splenectomy is of limited value except in cases of primary hypersplenism.

It is emphasized that in patients with thrombocytopenic purpura and hemolytic anemia, failure of an adequate course of hormone therapy to elicit a response prior to operation does not necessarily indicate that splenectomy will be of no benefit. Nor does this mean that the hormones may not be used successfully following surgery, should the latter prove a failure. In this connection, it should be pointed out that in hemolytic anemia, maintenance therapy on these drugs may generally be carried out at a lower dosage level than in thrombocytopenic purpura.

In the 25 patients treated with hormones who were reported in this series, no instance of adrenal failure either during or after operation was encountered, in spite of the fact that these agents were usually not given in the immediate postoperative period. Thus far no interference with wound healing has oc-

curred. The only deleterious effect of the administration of these hormones postoperatively was observed in 1 patient with pneumonia—apparently made worse by the use of cortisone, despite the concomitant use of antibiotics.

SUMMARY AND CONCLUSIONS

The results of the combined use of splenectomy, cortisone, and/or ACTH in 25 patients with various blood dyscrasias are reported. The effects of splenectomy alone in 21 similar additional patients undergoing operation during the same period of time are summarized. While strict comparison of the two series is not possible because of the selectivity employed in the cortisone-treated patients, analysis of these data supports evidence now accumulating in the literature that the use of these hormones in conjunction with splenectomy may be not only beneficial but perhaps also lifesaving.

This combined form of therapy was used in 14 of 22 patients with thrombocytopenic purpura subjected to splenectomy. Among the 14 in which drugs were used, these agents produced a satisfactory remission in 5, symptomatic improvement in 5, and no effect in 4. Of 12 patients undergoing splenectomy for hemolytic anemia, the hormones were used in 6. Their effect was beneficial in 2, probably lifesaving in 1, and of no assistance in 3. Five of 12 additional patients subjected to splenectomy for other forms of hypersplenism also received drug therapy. In only 1 of these 5 was the response to hormone therapy beneficial.

These data, together with a review of those recorded by other observers, indicate that in selected cases of thrombocytopenic purpura and hemolytic anemia, cortisone and/or ACTH may be used to advantage both preoperatively in preparing patients for splenectomy and postoperatively in tiding individuals over a recurrence when surgery fails or is otherwise unsatisfactory.

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DISCUSSION

DR. J. ENGELBERT DUNPHY (Boston, Mass.).—Our experiences in a much smaller number of cases have been very similar to those of Dr. Elliott. We have had some interesting experiences with very elderly patients in the 75- to 80-year-old range with relatively bizarre forms of so-called hypersplenism in which ACTH has been extraordinarily helpful in elucidating the nature of the situation, for example, in two patients with unexplained anemia, severe leukopenia, and recurrent infections. Following therapy with ACTH they have been restored to a suitable state for surgery and have remained well for long periods of time following splenectomy.

He made one comment that I would question. He said that the drugs were stopped, that is, cortisone and ACTH, the night before surgery and, of course, I am sure that if the patient had been on cortisone for a long period of time, they would not do that because of the fear of adrenal insufficiency.

Finally, I think it most important that this Society in its formal discussion take cognizance of the really very beautiful presentation that Dr. Roberts gave. It is a very important and fundamental contribution to our understanding of various fluid and electrolyte shifts which at the moment are confusing to the "superscientist" as well as to "Dr. Chips." I am certain that this kind of study will lead to practical applications of the greatest importance.

DR. EARLE BARNES MAHONEY (Rochester, N. Y.).—I would like to comment on one phase of this problem. During the past four years we have performed splenectomy on about twelve patients with acquired hemolytic icterus. These patients have been operated upon at the time of a hemolytic crisis and all had failed to respond to ACTH therapy. Most of them were critically ill, and the operation was performed as an emergency procedure. Seven patients have had no recurrence during the period of observation. One died forty-eight hours postoperatively because of continuing hemolysis. The remainder have had minor relapses which have so far responded to ACTH.

It is too soon to assess the results of splenectomy in this group of patients, but splenectomy does appear to be of value in those patients who have not responded to medical therapy. These patients are being carefully followed by Dr. Lawrence Young of the department of hematology at Strong Memorial Hospital and will be reported in detail at a later date.

DR. EDWIN H. ELLISON (Columbus, Ohio).—The speaker is certainly to be congratulated on his excellent results in these extremely ill patients. As he has indicated, ACTH and cortisone have influenced the indications for splenectomy, although not as much as originally postulated. With the assistance of Dr. Doan and Dr. Wiseman, we have just completed a review of our experiences with splenectomy for hypersplenism since 1946 at the Ohio State University Medical Center. A total of 275 patients with what we prefer to call dysplenism have been operated upon. Of these, 158 were classified as primary with a mortality of 1.9 per cent. The over-all mortality approximated 4.7 per cent. We were particularly interested in determining the over-all effect of cortisone and ACTH as the indication for splenectomy. Our experience parallels that of the men who have already spoken this morning. Until 1952 we had averaged some forty-two splenectomies per year. During 1952, the peak year for cortisone and ACTH, the number fell to thirty-one. In 1953, however, the number almost doubled and totaled sixty patients. Many of them had received one of the adrenocorticoids previously and were operated upon after recurrence of their disease.

All told, 101 patients with thrombocytopenic purpura have been subjected to splenectomy. I would like to call to your attention the tremendous deficit in blood volume in these patients suffering from a chronic bleeding disease. In many instances, the deficit

approximated 40 per cent and points up the value of preoperative transfusion. If one plans to use cortisone in these patients, it should be realized that not infrequently there is a delay in platelet response. This important observation means more when one considers the fact that 4.5 per cent of our patients with thrombocytopenic purpura come to operation having already had a cerebral hemorrhage. Further delay may increase the incidence of this unfortunate complication. In 1952 only ten patients with thrombocytopenia came to splenectomy. Of these, one-half had received cortisone and were classified as failures of drug therapy. Two of these five were operated upon as emergencies since their blood platelets had fallen to zero in spite of cortisone treatment, and one of these had suffered a cerebral hemorrhage during the interval.

The problem of associated disease is worthy of consideration when planning cortisone therapy for acquired hemolytic anemia. Although gallstones of the pigment type occur in about 16 per cent of all patients with congenital hemolytic anemia, the incidence rises to 40 per cent in the acquired group, and of these, 43 per cent have common duct stone and 14 per cent have recovered from at least one attack of acute pancreatitis. These findings are indication enough for operative intervention even in the absence of hemolysis and should be considered when planning therapy.

In closing, I would like to make one additional point in favor of operation for thrombocytopenic purpura. During the last year, twenty-two patients were operated upon for primary thrombocytopenias. The diagnosis had to be changed to secondary hypersplenism in five of the twenty-two patients following microscopic study of liver and lymph node biopsies, which are taken routinely following splenectomy. This finding is of considerable import both in prognosis and in planning future treatment of such patients and would have gone undiagnosed without operation.

DR. ROBERT ELLIOTT (Closing).—I rise to thank the discussers.

The point raised by Dr. Dunphy regarding the prolonged use of cortisone before operation is certainly important. One should indeed be cautious about the withdrawal of this drug when it has been given over a long period of time. That is one of the reasons why we gradually replace it with ACTH before splenectomy. We feel that the adrenal stimulation induced by this latter drug is important in the immediate preoperative period.

I am also glad that Dr. Mahoney has brought out the matter of postsplenectomy response to these drugs. We have had the same impression as he; that is, that following removal of the spleen in some patients with acquired hemolytic anemia previously treated with these agents, it has seemed that the response to the drugs is better than that obtained before operation.

Dr. Ellison's remarks were very interesting indeed, and I think his point about cerebral hemorrhage was well taken. If one looks through the literature, it will be found that in thrombocytopenic purpura, irrespective of whether splenectomy is performed or not, the incidence of cerebral hemorrhage runs as high as 13 per cent in some series. I do not think that this fact is widely appreciated. Therefore, one should be on guard against this complication even though one is giving these hormones before splenectomy.

QUANTITATIVE EVALUATION OF MITRAL COMMISSUROTOMY BY MEANS OF A STANDARDIZED EXERCISE TOLERANCE TEST

I. Evaluation of Method and Results*

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With the Assistance of James J. Pampush, M.D.,** and
Elizabeth Sherson, R.N.

(From the Departments of Medicine and Surgery, University of Washington School of Medicine)

RHEUMATIC heart disease is chronic pancarditis, both clinically and pathologically. The relative involvement of the pericardium, myocardium, and the valvular structures varies from individual to individual, however, and each component may exert a handicap, in terms of over-all cardiac function, that fluctuates from time to time. Operative procedures directed toward the correction of the valvular deformities of rheumatic heart disease cannot be considered curative operations, despite the fact that the patient's major disability may appear to be related to valvular pathology when seen by the surgeon. Hence a surgeon is operating primarily to relieve disability, and not necessarily to achieve a cure of an acquired defect. Therefore it becomes increasingly important for the surgeon, in order to treat *disability*, to measure it first in objective terms so that the results of operative intervention may be accurately and objectively evaluated.

Unfortunately it has been difficult to assess disability and total functional capacity in objective terms. Various laboratory measurements, while instructive with regard to limited functions, have not been satisfactory in this regard. A recent report by Andrus and associates[1] points out the well-recognized clinical fact that the best test of improvement following treatment for a disabling lesion is the patient's ability to meet the requirements of ordinary daily life. Hence measurements of single physiologic factors frequently are given importance which seems disproportionate to their actual significance to total functional capacity. Furthermore, these measurements usually are made with the patient at rest. This fallacy is related to the desire for oversimplification of a complex and difficult problem in evaluation of functional capacity.

If one considers the concept that in acquired heart disease our sights should be gauged, in most instances, to the relief of disability and accepts the thesis that disability per se represents a composite picture of the interrelation and integration of many compensating factors, then the importance for objective evaluation of the total physical fitness of the patient becomes

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**Trainee of the National Heart Institute, 1952-1953.

apparent. Furthermore, in this framework of reference, measurements at rest may give little insight into the disability which exists during activity. If disability is so severe that absolute bed rest is a necessity, in most instances the patient is not a surgical candidate.

In our experience, the Physical Fitness Index has proved to be a valuable method of assessing a patient's functional capabilities objectively as a means of establishing a preoperative base line and benefits which may be attributable to medical and surgical therapy.[2, 3]

The present report concerns itself with a series of patients with rheumatic heart disease submitted to mitral valve surgery in which the Physical Fitness Index (PFI) has been used as a measure of functional evaluation.* While this report concerns patients with surgical mitral stenosis, the applicability of this methodology is broad and may be utilized for the evaluation of other cardiac operations directed toward the relief of disability.

METHOD OF STUDY

The evaluation of each patient included history, physical examination, chest fluoroscopy and radiography, electrocardiograms, and ancillary laboratory tests. Many of the patients were subjected to cardiac catheterization both preoperatively and postoperatively. The functional status was determined by two or more observers in accordance with the criteria of the New York Heart Association. All patients were studied by a standardized exercise tolerance test which forms the basis for the derivation of the Physical Fitness Index.[3]

The exercise tolerance test may be considered to consist of three parts: the rest, exercise, and recovery periods. Throughout all three portions of the test, observations at one-minute intervals are made of the blood pressure, heart rate, respiratory rate, "respiratory efficiency" (difference between oxygen concentration of inspired air and expired air), and electrocardiogram (precordial lead). The appearance of symptoms and changes in physical signs resulting from exercise is noted as well.

Initially, the patient is observed routinely for four minutes while sitting at rest, one minute of standing, ten minutes of walking, and five minutes of recovery while sitting. The exercise phase of the exercise tolerance test consists of the patient's walking on a treadmill at a rate of 1.7 miles per hour on a 10 per cent grade for ten minutes or less, depending upon the capability of the patient.

The Physical Fitness Index is derived from the following formula[3]:

$$\text{PFI} = \frac{\text{Endurance}\dagger \times \text{Respiratory efficiency}\ddagger \times 100}{\text{Total three-minute recovery heart rate}\S}$$

The normal range of the Physical Fitness Index is 13 to 26, with an average of 19. An overlap may exist in the lower ranges in patients with cardiac abnormalities and in normal patients. It has been previously demonstrated that for each patient with mitral stenosis, not only are the individual components of the formula reproducible but, as a corollary, the Physical Fitness Index is likewise reproducible.[2]

All patients have been studied by exercise tolerance when initially seen. Several have been restudied intermittently after medical management preoperatively. Most of the survivors have been studied intermittently and some for over two years following commissurotomy.

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*This too may represent an oversimplification. Nevertheless it is an approach to the evaluation of functional capacity in objective terms based upon the ratio of endurance to a standardized stress, efficiency of oxygen extraction, and circulatory recovery.

†Number of minutes walked on the treadmill.

‡Difference between inspired and expired oxygen concentration (during exercise by means of a continuous recording Beckman oxygen analyzer).

§Total number of beats in the three minutes following exercise regardless of duration.

CASE MATERIAL

Since the beginning of this study, fifty-one patients have been submitted to mitral valve surgery. Only forty-eight have been tested by exercise tolerance. In three patients, deformities secondary to peripheral embolization precluded walking on the treadmill. In general, this series was similar to others reported. Women predominated in a 3:1 ratio. The extremes in age were 19 to 65 years, with the average age of 39.5 years. Fifty-three per cent had auricular fibrillation. Nine patients had a total of fourteen peripheral embolic episodes in the natural course of their disease. There has been no peripheral embolization at the time of surgery.

The case material presented is conditioned by our indications for surgery. These may be briefly summarized as follows: (1) patients with mitral stenosis who are disabled, (2) women with mitral stenosis in the child-bearing age who have had heart failure during a previous or existing pregnancy, and (3) patients with auscultory evidence of mitral stenosis who have exhibited one or more episodes of peripheral embolization and have radiographic evidence of a prominent appendage of the left atrium that might have been the source of emboli. Such patients need not be disabled, however.

THE RESPONSE PATTERN TO EXERCISE

The response of a normal individual during exercise tolerance tests is compared with a typical response of a patient with mitral stenosis pre- and postoperatively in Fig. 1.[2]

The normal control subject responds to exercise by a moderate elevation of pulse and increased pulse pressure due mainly to an increase of the systolic component, a simultaneous rise in respiratory rate, and an improvement in "respiratory efficiency," that is, oxygen extraction. Following exercise, all elements are restored to the control resting valves within the first one to three minutes of the recovery period.

By contrast, the patient with mitral stenosis may be unable to walk the full ten-minute period. The pulse rate increases markedly and quickly. With tachycardia, the duration of diastolic filling between each beat is shortened and the stroke output and systolic blood pressure may decrease. This decrease may be progressive as exercise continues. As the blood mass increases behind the valvular block, an excessive increase of the respiratory rate results, accompanied by a paradoxical decrease in oxygen extraction, which may be secondary to the congested pulmonary vascular tree. Frequently, a marked depression of the ST segment and inversion of the T waves of the electrocardiogram, compatible with myocardial ischemia, are noted.

In the recovery phase, the blood pressure frequently rebounds above the resting base line level. This phenomenon, while frequently observed in patients with mitral stenosis, has been noted in patients with other cardiac diseases as well.[4] An explanation is not readily available. It should be noted further that the return to normal of the other factors observed is delayed. Particularly is this true of the recovery heart rate.

In Fig. 1, the benefit derived from ideal medical management is well depicted. The PFI was stabilized at this level. Upon repeated study, the result was reproducible. Consequently the patient was considered to be at

her peak of physical fitness, and further medical measures were found to be unrewarding. Therefore surgery was carried out at a period when the patient was best able to tolerate it. A satisfactory surgical result was obtained, as evidenced by considerable clinical improvement and a further increase in the patient's Physical Fitness Index. The return to a more nearly normal response to exercise can be readily appreciated by inspection of the individual elements measured in this patient compared to the normal subject.

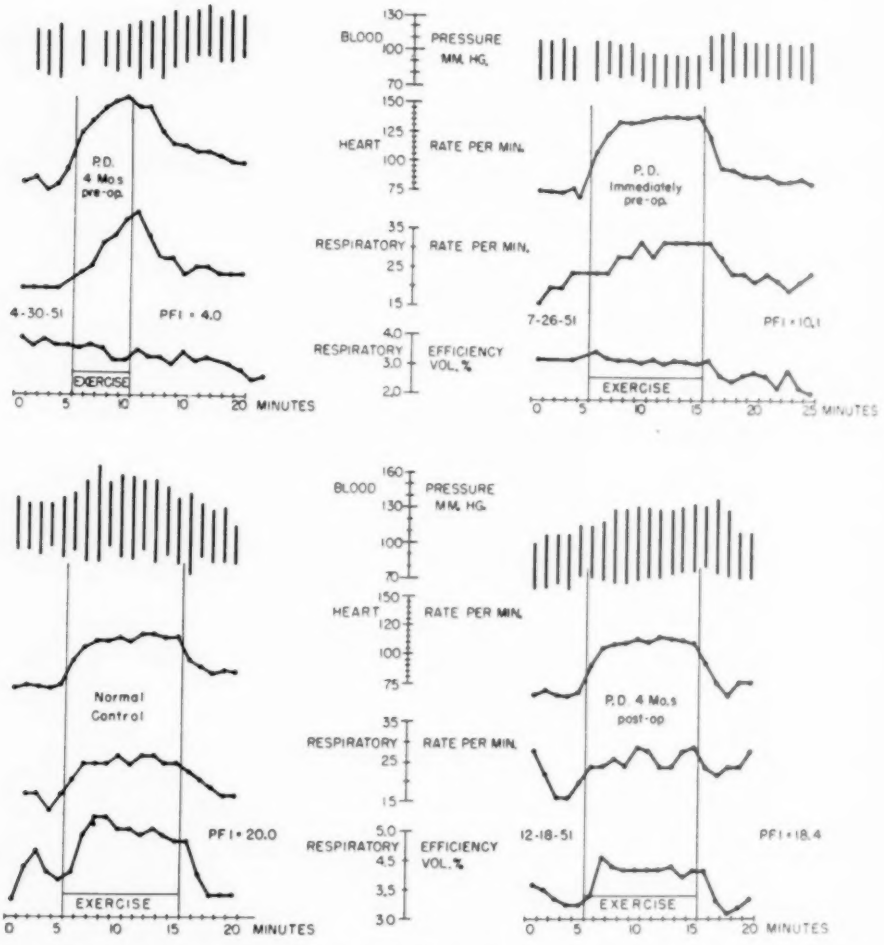

Fig. 1.—Physiologic responses of a patient, P. D., with mitral stenosis to the standardized exercise tolerance test. Preoperative results initially in upper left quadrant, and after medical treatment in upper right quadrant. Postoperative results at four months are shown in lower right quadrant. A representative normal control subject is shown in lower left quadrant. (From Bruce and Rodgers,[2] with permission of the American Journal of Medicine.)

RESULTS

Relationship of PFI to Clinical Evaluation.—Inasmuch as patients being submitted to cardiac surgery are evaluated universally according to the clinical appraisal of the functional capacity, it is important first to ascertain the relationship of the PFI to this evaluation. Hence the patients will be considered in relation to each of the four categories commonly employed. (Fig. 2.)

Class I patients: Only two patients in Class I were submitted to mitral valve surgery. Neither was operated upon on the basis of disability, but rather for the third indication, namely, history of emboli. The initial mean PFI of 12.4 increased to 14.6 as a result of preoperative medical treatment (see Table I). The postoperative course showed progressive increments in mean PFI up to one year.

Class II patients: There were six patients in Class II, of whom only five had any disability immediately prior to surgery. The other patient was operated upon because of the second indication, namely, congestive heart failure during pregnancy. Following parturition, she was symptom free.

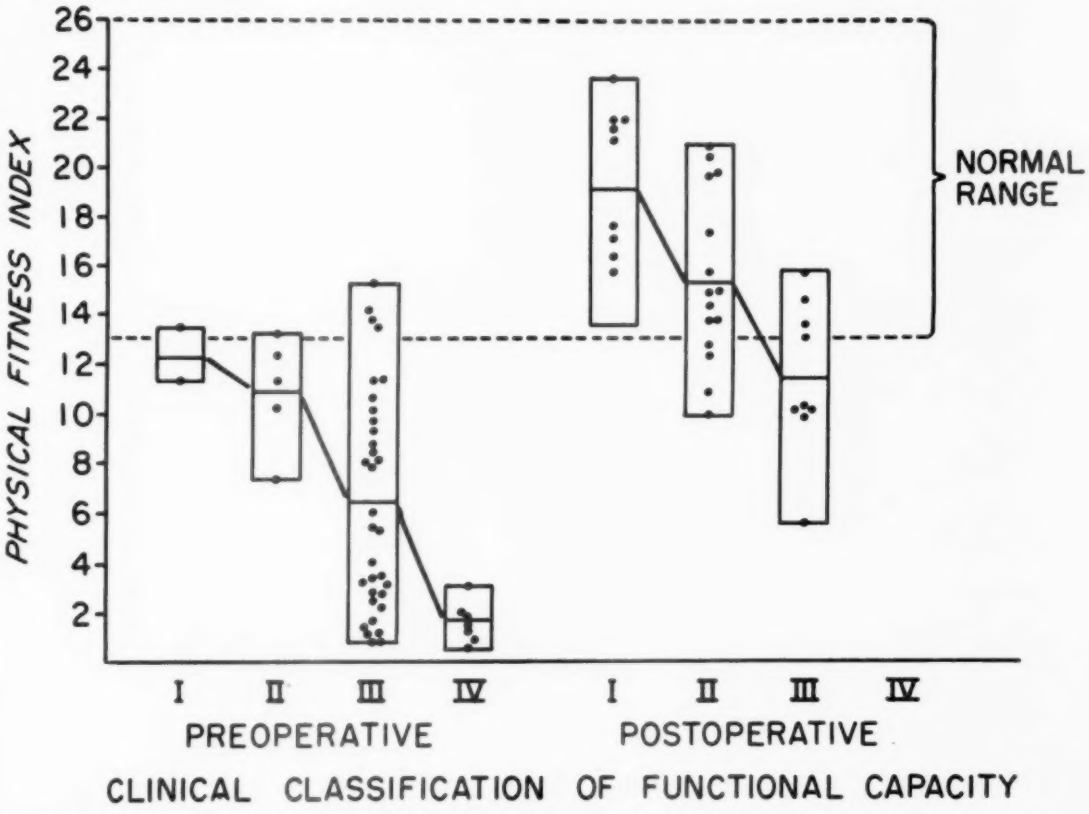

Fig. 2.—Comparison of clinical classification of functional capacity and Physical Fitness Index. Preoperative data on left and postoperative data on right.

Again the mean PFI increased from 10.7 to 14.7 as a result of preoperative medical treatment. The initial postoperative evaluation revealed a mean PFI of 17.2 within the first three months, but the subsequent evaluations revealed lower values.

Class III patients: There were thirty-three patients in Class III who were submitted to surgery because of the primary indication of disability and, also, in some instances because of the second indication of a positive history of repeated emboli.

On the average these patients exhibited a negligible increase in the mean PFI as a result of preoperative medical treatment. A few even showed slight deterioration. In general, postoperatively they tended to exhibit a prolonged convalescence and slow increase in functional capacity. The mean PFI was

TABLE I. QUANTITATIVE EVALUATION OF MITRAL VALVE SURGERY (EXPRESSED IN TERMS OF THE PHYSICAL FITNESS INDEX)

INITIAL CLINICAL CLASSIFICATION	NUMBER OF PATIENTS	AGE MEAN (RANGE)	PREOPERATIVE PFI		POSTOPERATIVE PFI				DURATION OF FOLLOW-UP MONTHS MEAN (RANGE)
			INITIAL MEAN (RANGE)	FINAL MEAN (RANGE)	0-3 MONTHS MEAN (RANGE)	3-12 MONTHS MEAN (RANGE)	1-2 YEARS MEAN (RANGE)		
I	2	31 (26-35)	12.4 (11.3-13.4)	14.6	15.0	17.6 (15.6-19.6)	21.8		16.5 (8-25)
II	6	33 (19-47)	10.7 (7.3-13.1)	14.7 (12.4-14.9)	17.2 (14.8-19.6)	13.7 (10.0-17.6)	9.4		7 (3-15)
III	33	41 (26-65)	6.2 (0.8-15.2)	7.3 (1.8-13.5)	9.7 (1.3-16.7)	13.6 (5.1-23.4)	14.9 (9.9-21.8)	12	(3-24)
IV	7	35 (24-39)	1.6 (0.6- 2.9)	4.7 (2.3- 6.6)	8.8 (6.0-10.8)	16.8 (13.0-20.4)	9.0	9	(4-15)
Total	48	41 (19-65)	6.3 (0.6-14.1)	8.5 (2.2-19.7)	10.4 (1.3-19.6)	14.2 (5.2-23.4)	14.5 (9.0-21.8)	12	(3-25)

9.7 within the first three months and then showed a greater rise to 13.6 for the period of three to twelve months. There was usually little further substantial improvement after the first year (PFI 14.9).

Actually these patients in Class III could be subdivided into two groups postoperatively (Table II). Six patients (18 per cent) exhibited a substantial improvement clinically within the first three months. The remaining twenty-seven (82 per cent) did not have an excellent improvement initially; in fact, convalescence tended to be prolonged. The mean PFI for the former group was 14.7 within three months, whereas the mean PFI value for the latter group was 7.4 for the corresponding period of time. (See Table II.)

TABLE II. VARIATIONS IN RATE OF IMPROVEMENT IN CLASS III PATIENTS POSTOPERATIVELY

	INITIAL POSTOPERATIVE RESPONSES	
	"GOOD"	"POOR"
Number of patients	6(18%)	27(82%)
Mean PFI		
Initial preoperative	3.2	6.8
Final preoperative	6.4	7.7
Within 3 mo. postoperative	14.7	7.4
Within 3-12 mo. postoperative	16.6	12.3
Within 1-2 yr. postoperative	19.3	13.2

Furthermore, there was a conspicuous difference between these two groups of patients with respect to subsequent deterioration of functional capacity clinically and the objective appraisals with respect to physical fitness.* Those with an excellent response initially had a mean PFI of 9.7 on the average of nine months after operation. The others with delayed improvement had a mean PFI of 5.4 about the same time, on the average. In most instances the subsequent deterioration in functional capacity was more or less reversible as a result of more intensive medical treatment with respect to rest, increased amounts of digitoxin, and, in some instances, the use of diuretics. Hence cardiac insufficiency appeared to be an important factor, as noted previously.[2]

Finally, with respect to age, the mean age of the former group of six patients with initial excellent responses to surgery was 34 years, whereas the mean age of the latter group of twenty-seven patients with prolonged convalescence and moderate improvement was 43 years. Hence it is possible that the increased age of one group contributed to the delayed and limited improvement from mitral valve surgery.

Class IV patients: There were seven patients in clinical Class IV when initially evaluated for mitral valve surgery. The initial PFI of 1.6 increased to 4.7 as a result of preoperative medical treatment. Most of these patients received oxygen treatment for a few days prior to operation, in addition to bed rest, digitoxin, diuretics, and low-salt diet.

Only three patients have been followed for four to fifteen months postoperatively. The mean PFI increased to 8.8 within the first three months and to 16.8 within one year, confirming the clinical evidence of very substantial improvement.

Over-all Changes in Functional Capacity and PFI: The maximal change in all patients with respect to clinical classification is shown in Fig. 2, where the initial preoperative status is compared with the best postoperative status. Ten patients (21 per cent) attained a Class I rating with a mean PFI of 18.9. Fifteen patients (31 per cent) improved sufficiently to be categorized as Class II; their mean PFI was 15.2. There were nine patients (19 per cent) in Class III, with a mean PFI of 11.3, and no surviving patients remained in Class IV.

*Thus far, no satisfactory correlation with auricular biopsy material has been made to establish the relationship, if any, to these different postoperative courses.

Comparing the initial preoperative evaluation with the best postoperative performance revealed an average increase in functional capacity in the entire series from Class III to Class II ($P < 0.001$). This apparent change clinically was accompanied by a mean increase in PFI from 6.3 to 14.9, amounting to a difference of 8.6 ($P < 0.001$).

It is noteworthy that the mean PFI values postoperatively were considerably higher than preoperatively for Classes I, II, and III patients (Fig. 2). Any attempt to offer completely satisfactory explanations of this phenomenon would be only speculative. However, there was no striking difference in the ranges of variation postoperatively, possibly because the three groups were more nearly of equal size. The increase in mean PFI values in Class I, II, and III patients postoperatively reveals the lack of a completely satisfactory correlation between the subjective appraisal of patient and physician and the physiologic response to a standardized work load.

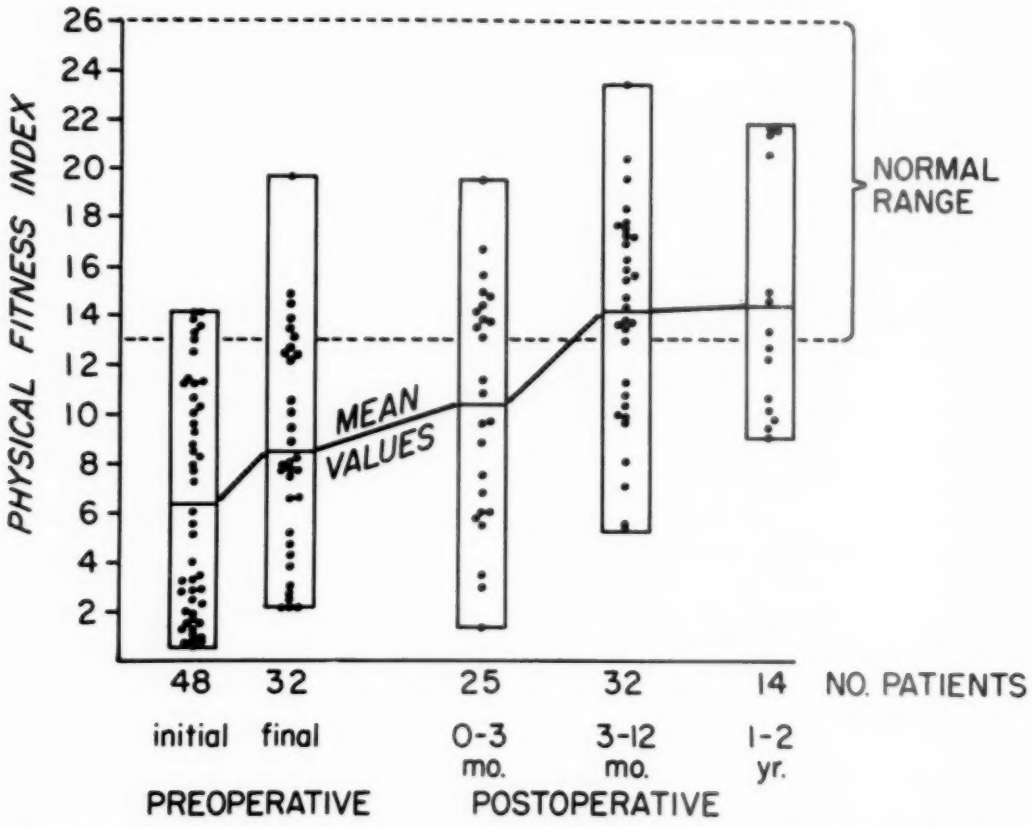

Fig. 3.—Results of mitral valve surgery. Quantitative effects of medical and surgical treatment of patients with mitral stenosis.

Effects of Treatment on Physical Fitness.—The quantitative effects of further bed rest and medical treatment preoperatively, as well as the rates of changes postoperatively, are shown in Fig. 3. In comparing the PFI values in thirty-two patients initially with their final preoperative score, there was an increase from a mean of 5.6 to 8.5, which was not significant ($P < 0.02$).*

*Data are available on twelve other control patients who were not submitted to surgery and were evaluated again about one year later.[5] In this group, the PFI increased from a mean of 9.3 to 12.0, which was also not significant ($P < 0.02$).

When consideration is given to individual cases, the degree of improvement gives an indication of the increase in that particular individual's reserve. On the other hand, some patients prior to consultation have already been on ideal medical management and did not improve further. However, the failure to improve did not necessarily imply that the patient would not withstand surgery, nor be improved by operation in the event that a proper valvular lesion was present.

As a result of mitral valve surgery, the mean PFI increased to 10.4 ($P < 0.001$) for twenty-five patients re-examined within three months, and increased further to 14.2 ($P < 0.001$) for thirty-two patients studied from three to twelve months after operation. Fourteen patients have been followed for one to two years after surgery and these have a mean PFI of 14.5, indicating, on the average, no further improvement. Although the PFI in many patients increased sufficiently to be in the normal range, the mean of 14.5 was still appreciably below the mean of 19 observed in normal adults.[3] In fact, these mean postoperative values were less than the average PFI of 16.5 observed in nineteen patients (9 to 42 years of age) observed from two to fourteen months after an attack of acute rheumatic fever.[4] Furthermore, the additional mean improvement gradually obtained by some patients has been canceled in other patients by the subsequent deterioration of functional capacity due to recurrent heart failure or other factors. These variations in response will be considered in detail elsewhere.[6]

Relationship of PFI to Operative Risk.—There were four deaths in this series. Two occurred in Class III and two occurred in Class IV patients. All were known to have poor reserve and high mortality risk preoperatively. In fact, all four of these patients were kept in an oxygen tent for the two to four days preoperatively in order to increase their cardiac reserve. The PFI values ranged from 1.1 to 2.9 when tested. The exercise test was repeated in two of these patients and exhibited a negligible increase as a result of this therapy.

Although impaired cardiac reserve cannot be held entirely responsible for the deaths that occurred, it is more than likely that some of these patients succumbed partly because of this low reserve and inability to withstand the functional consequences of complications.

One patient died of subendocardial infarction and ventricular fibrillation at operation (calcified auricle; superior vein approach). Two others died of hyponatremia, complicated by metabolic acidosis and pulmonary edema in one patient as well as pulmonary embolism and edema in another patient. These deaths occurred on the sixth and ninth days postoperatively, respectively. The fourth fatality occurred on the thirteenth day as a result of bronchial obstruction from inspissated mucus.

Relationship of PFI to Hemodynamic Changes.—A series of fifteen patients subjected to cardiac catheterization preoperatively were intensively evaluated again five to twenty-two months (average 13.4 months) after operation.[7] All were improved subjectively. The incidence of symptoms and appearance of congestive heart failure and other complications subsided in most. Whereas twelve of these fifteen patients required daily rest periods preoperatively, only six still continued this habit postoperatively. (Table III.) The heart size diminished in nine and the manifestations of failure decreased in all but one. Only ten, instead of all fifteen patients, still used digitalis. When re-evaluated by means of cardiac catheterization, the only significant changes in all the parameters was a reduction in "pulmonary capillary" (wedge) pressure and an increase in mitral valve orifice (Table III). A slight increase in resting stroke volume and a slight decrease in pulmonary arterial pressure had only borderline significance.

The data obtained from serial exercise tolerance tests in these fifteen patients were highly instructive. The relative intensity of dyspnea and fatigue during

this standardized stress diminished ($P < 0.01$ and < 0.001, respectively). The mean endurance, exercise respiratory efficiency, and average systolic blood pressure during exercise increased (Table III). The greatest change of all was in the PFI. Despite improvement in these cardiorespiratory functions, there was a slight increase in the incidence of precordial electrocardiographic abnormalities during exercise.

TABLE III. RELATIONSHIP OF EXERCISE TOLERANCE TO HEMODYNAMIC CHANGES IN FIFTEEN PATIENTS

	Before	*After*	P
A. Distribution of Patients According to Clinical Classification			
Class I	0	2	
Class II	1	7	
Class III	12	6	
Class IV	2	0	
B. Mean Values of Salient Laboratory Data*			
Rest (cardiac catheterization)			
PC pressure, mm. Hg	29	19	<0.001
Mitral valve orifice, cm.^{2}	0.7	1.7	<0.001
Stroke volume, ml.	46	68	<0.01
PA pressure, mm. Hg	49	30	<0.01
Exercise (treadmill)			
Endurance, minutes	5.1	9.7	<0.001
Respiratory efficiency, vol. %	3.27	4.29	<0.001
Systolic BP, mm. Hg	124	145	<0.001
PFI	4.9	13.3	<0.001

*None of the other variables, such as cardiac output, oxygen saturations, pressures, and so forth showed P values less than 0.02.

It is apparent, therefore, that the PFI is a valid measure of functional capacity in patients with rheumatic heart disease. This technique of exercise tolerance testing yields results that are valid and easier to obtain under standardized conditions than those derived from cardiac catheterization.

DISCUSSION

Heretofore the evaluation of cardiac surgery has been based largely upon the clinical appraisal of symptoms, changes in physical signs, and changes in ancillary laboratory observations. Since none of the laboratory data has permitted a completely satisfactory appraisal of the total functional capacity, reliance has had to be placed upon the patient's ability to withstand the ordinary demands of daily living. This, however, has been difficult to quantitate. This is understandable, for it takes at least two individuals to make such an evaluation, namely, the patient and the physician. Usually both individuals are interested in obtaining a good result which may influence the final appraisal. It is important, therefore, to have some objective test as a point of reference for an evaluation of the total functional capacity. Such a test must involve a standardized work load in order to evaluate functional capacity. This consideration is particularly important in evaluating patients with rheumatic heart disease because of the changing importance of the various components of chronic pancarditis with respect to disability.

The standardized exercise tolerance test provides a method for quantitatively describing the changes in functional capacity of patients submitted to mitral valve surgery. Although many salient observations are made routinely during the

performance of the test, a final integration of physical fitness can be expressed in terms of the Physical Fitness Index. This index is a ratio of the product of endurance and oxygen extraction during effort to the rapidity of circulatory recovery following exertion. The PFI has been shown to correlate with the clinical appraisal of functional capacity. That is to say, Class I cardiac patients have a higher PFI value than Class IV patients, and Classes II and III occupy intermediate and overlapping ranges. Furthermore, reproducible results can be demonstrated with this technique. The rather wide scattering of results with respect to any particular class of patients reflects the considerable variation in evaluation of functional capacity with respect to clinical criteria.

When the standardized exercise tolerance test is employed to evaluate changes in functional capacity, it is possible to quantitate the amount of improvement from medical treatment preoperatively. Although this was striking in some patients and lacking in others, the over-all trend revealed a change of only borderline significance (P 0.01-0.02). Similar evaluations postoperatively revealed a significant improvement ($P < 0.001$), especially for the period of three to twelve months postoperatively. Furthermore the rate of changes and any late improvement could be determined also. Thus it was possible to differentiate the postoperative course of a minority of Class III patients who obtained excellent results from the majority who exhibited a protracted convalescence and less striking improvement in functional capacity.

It is of great interest to observe a change in the relationship of the PFI to the clinical classification of functional capacity postoperatively. Although no definite explanation has been established, the question is raised as to whether there is a change in the threshold of subjective awareness of symptoms postoperatively. Possibly some patients have become conditioned to the limitations of chronic illness and disability and tend to minimize their complaints. Then, being substantially improved by surgery, they live on a different plane, where they may be symptom free part of the time. At other times, and with some unaccustomed exertion, they become unduly aware of their symptoms and in a sense may exaggerate them, at least with reference to their previous preoperative experience.

The relationship of the PFI to operative mortality is also of interest. Although two of the four patients who died as a result of surgery were thought to be Class III clinically, all exhibited PFI values of less than 3.0. This, of course, does not indicate that all patients with a very low PFI are not candidates for surgery, but it does indicate that they have very limited reserve to withstand the effects of even minor complications that may develop at operation or during the postoperative course.

Finally, although a small group of patients exhibited substantial improvement clinically and by means of the standardized exercise tolerance test approximately one year postoperatively, the hemodynamic studies obtained by cardiac catheterization revealed significant improvement in only a few of the variables. They were the reduction in resting pulmonary capillary and pul-

monary arterial pressure, as well as the increase in size of the mitral valve orifice and stroke volume. These changes were, of course, the ones that should be observed if the surgical procedure had been accomplished successfully.

SUMMARY

Attention has been drawn to the Physical Fitness Index as a methodology for the evaluation of cardiac disability and its alteration secondary to medical and surgical therapy. This approach allows the physician the opportunity to quantitate functional capacity in an objective manner. A comparative study has been presented of other methods of evaluating the patient in relationship to the Physical Fitness Index. The Physical Fitness Index appears to define better the true functional status of the patient.

By the utilization of this means of evaluation, we have gained a better understanding of the relationship of mitral valve surgery to rheumatic heart disease. While this study has been concerned with rheumatic heart disease, the extension of this method in the evaluation of surgical procedures for other types of acquired heart disease is suggested.

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DISCUSSION

DR. JAMES DANIEL HARDY (Memphis, Tenn.).—I rise primarily to say that this is a beautiful study. The operation has come of age, as we are now willing to examine the results in a quantitative manner. I would like to ask one question. Will Dr. Merendino please comment upon his conclusions concerning the relation of difficulties encountered at operation, such as the presence of marked calcification of the valve, to the follow-up results—if these correlations have been attempted?

DR. W. G. BIGELOW (Toronto, Ontario).—Mr. Chairman, it is very interesting to hear the report of such a careful analysis of results from the surgery of mitral stenosis.

The matter of analyzing the results of this operation has been attacked from a somewhat different viewpoint in Toronto. When one is faced with the application of a new surgical procedure to a condition for which there has been no treatment of this type before, one would like to know something of the natural life history of the disease so that one may compare operative mortality against the expected prognosis.

Dr. W. F. Greenwood and Dr. J. K. Wilson have recently carried out a natural life history study of mitral stenosis from the case histories of 171 patients over a twelve- to fifteen-year period (to be published). They have used three milestones of the disease on which to base their observations. The first milestone is described as "severe pulmonary

congestion" and has been defined to describe the onset of attacks of acute pulmonary edema, orthopnea, or severe dyspnea brought on by climbing one flight of stairs or walking one block. The second milestone was the onset of auricular fibrillation, and the third the onset of right heart failure.

I do not have their exact figures with me for the fifteen-year follow-up; however, from the onset of "severe pulmonary congestion," 17 per cent of these patients were dead within six months and similarly 17 per cent were dead within six months from the onset of auricular fibrillation. From the onset of right heart failure 25 per cent were dead within six months.

A group of patients with definite mitral diastolic murmurs and no symptoms were followed as well over the fifteen-year period.

Now, in assessing the results from operation in the light of this natural history study, which is not completely reported here, one may first say that there would appear to be justification for our present-day basis for selecting cases for surgery. It justifies our not operating upon the symptomless group as we cannot improve upon their prognosis.

In the light of what was said last evening, I hesitate to say that I have operated upon 150 patients with mitral stenosis. I do not know whether or not that places me over the "Dunphy threshold"! The first eighty-eight patients have been followed for seven months to four years and examined by the cardiologists. An exact comparison with the natural life history study will not be possible for a further eleven years. However, in those patients operated upon who would have fallen into the "severe pulmonary congestion" group there is a 3 per cent mortality rate from operation and no deaths after the first week postoperatively. That is a four-year follow-up, so the figures compare very favorably with those quoted previously of 17 per cent dead in six months. The right heart failure group experienced an operative mortality of 18 per cent with no deaths after the first six weeks postoperatively, and that of course compares very favorably with the natural life history of this group.

There may be a source of error in comparing these two groups of patients, but it is an attempt to analyze carefully the results from operation by a method with which we have the most experience, namely, clinical assessment of the patient. It would almost look as if it were more dangerous for the patient coming with these symptoms to live the next six months than it is to have the operation. If nothing else, this study may put the surgeon at ease in advising operation to some of the patients whom he sees.

The statistical results for surgery in patients who have experienced a peripheral embolus compared to the life expectancy of a patient who has had an embolus clearly justify the use of peripheral embolism as an indication for operation.

DR. G. H. A. CLOWES, Jr. (Cleveland, Ohio).—This paper contains a beautiful analysis of the functional problems presented by the cardiac patient who undergoes surgery upon the mitral valve. In the presentation of his data, Dr. Merendino mentioned that rheumatic fever and its sequelae involve not only the valves but all parts of the heart. We heartily agree that other forms of involvement, such as myocarditis, may influence the ultimate result of a surgical procedure. Furthermore, the lungs play a less-important roll in the functional outcome.

Last year we conducted an analysis of the pathologic state of the pulmonary arterioles in the lungs of patients who underwent mitral commissurotomy at the Cleveland City Hospital. A comparison of wall thickness to lumen showed that there was no correlation of the degree of sclerosis to pulmonary artery pressure. Yet the degree of arteriolar sclerosis correlated well with a product of both pressure and the length of time that symptoms had existed. However, the amount of sclerosis did not appear to influence the pulmonary function tests before or after the operation with the exception that people with severe sclerosis did not get their maximum benefit from operation for several months postoperatively. The amount of chronic passive hyperemia present in the lung biopsies was directly related to the depression of preoperative vital capacity.

I would like to ask Dr. Merendino whether he and his group have examined the lungs microscopically, and if so, what relation was found to the functional status of the patients?

DR. JOHANN L. EHRENHAFT (Iowa City, Iowa).—I have just a short comment and one question. I would like to congratulate Dr. Merendino for the very careful presentation and for his basis for evaluating postoperative patients following mitral valvuloplasty for mitral stenosis. Only very few studies along this line have been made, and in most places the postoperative patients were evaluated only on a clinical basis. Questions such as "Do you feel better? How much shortness of breath do you have now? What can you do? Can you do your housework now?" constituted nearly all of the evaluation except in patients who have had postoperative cardiac catheterizations. In this latter group, naturally definite proof for physiologic improvement can be gained. I concur with Dr. Merendino's statement that we only improve those patients and never cure them. I believe that patients who have mitral stenosis once will always have mitral stenosis of a certain degree even though they show marked clinical improvement postoperatively. At the University of Iowa Hospitals we have about ninety patients who have undergone mitral valvuloplasty for mitral stenosis. We have lost four patients in the postoperative period and there were no deaths in about three years in the surviving group.

I would like to ask one question. What does Dr. Merendino do about patients who have auricular fibrillation, either preoperatively or who develop auricular fibrillation in the postoperative period?

DR. MERENDINO (Closing).—I wish to thank Dr. Bigelow for his informative comments.

With regard to the questions, Dr. Hardy has inquired concerning the correlation of the result with the different types of valve encountered. Detailed records have been kept of the findings at operation. In our experience, valves with calcified lips have fractured easier than fibrous-lipped valves. Elastic-edged valves have, at times, filamentous webbing, agglutinating the cusps together. The latter are sometimes easily broken without the sensation of accomplishing a great deal. The surgeon in each case has attempted to estimate the eventual result. This estimation has been based not only upon the increased size of the mitral valve orifice, but also on the presence or absence of regurgitation before and after commissurotomy, the original intra-atrial pressure and that following mitral valve surgery, the age of the patient, and complications of the disease prior to operation. In short, the surgeon's appraisal results from a correlation of all possible facets of the problem. These estimations were catalogued as excellent, good, fair, and poor.

In those classified as excellent, there exists the closest correlation postoperatively with the patient's total functional capacity (PFI). However, there are notable exceptions to this in this group. One patient, who was thought to have the best commissurotomy of the entire series, has been in and out of heart failure for the past two years and is one of the poorer results. In those operations classified as good, fair, or poor, there appears to be little correlation with the PFI. Certain instances thought to be poor results were excellent; certain ones estimated as good were poor, and so forth.

This apparent lack of correlation of the surgeon's estimate of the anticipated result with the PFI of the patient accents the point stressed in the body of the paper, namely, that the operation is an incident in the course of the patient's illness. An attack has been made upon one important aspect of the disease, namely, the valve. However, there are other facets to the illness which condition the end result and not the extent of commissurotomy alone. At the same time, I do not wish to underestimate the value of commissurotomy when indicated.

With regard to Dr. Clowes' question regarding the status of the lungs, our experience would probably closely parallel his own. It is my feeling that certain changes observed

in the lung and arterioles are probably reversible. I can remember one patient who exhibited such a degree of pulmonary fibrosis by x-ray that the roentgenologist thought that miliary tuberculosis was present. This patient has obtained one of our best results. We have obtained, in practically all cases, both lung and auricular biopsies. Approximately 50 per cent of our patients have biopsy evidence of rheumatic activity.

Dr. Ehrenhaft has raised the question of what to do about atrial fibrillation. We have had little success with the conversion to normal sinus rhythm of patients with established atrial fibrillation. Little is gained by attempted conversion preoperatively. A few patients have been converted postoperatively with both clinical and objective benefit. Of those patients who have developed paroxysmal atrial fibrillation postoperatively, all have been converted to a normal sinus rhythm, although some still require maintenance dosages of quinidine. It has been our policy to attempt to convert these latter patients before they are discharged from the hospital.

There is a second point I would like to make concerning fibrillation. We have learned to be wary of the patient in Class III or IV with normal sinus rhythm, particularly patients who have borderline regurgitation, who may be suspected of having rheumatic activity without actual proof, or those who have lung pathology other than fibrosis. In our experience, these patients frequently break over into atrial fibrillation postoperatively in spite of all efforts to prevent it. When this occurs, superimposed upon the patient's other difficulties, a desperate situation sometimes develops. Contrary to the beliefs of others that atrial fibrillation with a controlled ventricular rate is an innocuous affair, we have shown deterioration of total functional capacity (PFI) with a breakover from normal sinus rhythm to fibrillation and the reverse, namely, an improvement of PFI, with the conversion of fibrillation to a normal sinus rhythm.

THE ROLE OF INTRACELLULAR AND EXTRACELLULAR ELECTROLYTES IN THE CARDIAC ARRHYTHMIAS PRODUCED BY PROLONGED HYPERCAPNIA*

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CATION exchanges between the extracellular and intracellular compartments of the body play an important role in the reaction of the experimental animal and human beings to changes in acid-base balance. The data of Darrow[1] and others[2-4] show that in chronic metabolic alkalosis, potassium tends to leave the cells and is replaced by sodium, whereas in metabolic acidosis, the potassium content of the intracellular compartment is increased. Recently, Cooke[5] has presented evidence that a similar relationship may be present in chronic respiratory acidosis and that the distribution of the cation is dependent upon the hydrogen ion concentration of the extracellular fluid. These conclusions have been derived from data obtained following relatively long periods of alteration in acid-base balance. On the other hand, Keating and associates[6] concluded that there was an over-all shift of potassium from the cells to the extracellular fluid during acute metabolic acidosis. They found that the plasma potassium varied inversely with blood pH as the latter was altered acutely in dogs by the intravenous infusion of ammonium chloride or sodium bicarbonate. The use of nephrectomized animals excluded any effects caused by altered renal excretion.

The nature and extent of the electrolyte changes during acute respiratory acidosis and their role in the resultant disturbances in physiology await further clarification. These changes may have considerable clinical importance since patients undergoing surgery frequently show severe retention of carbon dioxide.[7, 8] Suspicion has already been directed toward hypercapnia as a primary factor in the etiology of the cardiac arrhythmias and arrest which may occur during surgery.[9-11]

It has occurred to us that respiratory acidosis, in addition to augmenting the effects of vagal stimulation on the heart,[9] might also contribute to cardiac abnormalities by an effect on electrolyte metabolism. The present investigation is one of a series designed to study the effects of acute, severe respiratory acidosis on intra- and extracellular electrolyte composition and to correlate, if possible, associated electrocardiographic changes.

METHODS

Commercially bred adult male rats (Charles River strain) were fed ad libitum on Purina Chow. The rats were anesthetized with pentobarbital (30 mg. per kilogram) and were placed in a large desiccator. The chamber was aerated with a humidified mixture of 35 to 45 per cent carbon dioxide in oxygen flowing constantly from a large Douglas bag.

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The concentration of carbon dioxide was periodically checked by a modification of the Scholander method.[12] Electrocardiograms were obtained with the Sanborn Visocardiette, using No. 24 needles inserted subcutaneously as the electrodes. At the end of the experiment the atmosphere was rapidly reverted to that of room air by removing the desiccator lid and blowing air in with a fan. After an interval for electrocardiographic observation, the surviving animals were stunned by a blow on the head. The peritoneal cavity was opened and unhemolyzed blood was obtained from the aorta through a No. 18 needle into a heparinized syringe. The organs to be analyzed were then removed and appropriate amounts blotted lightly and weighed. The plasma and organs were analyzed as reported elsewhere, where the data are presented in more detailed form.[13]

The experiments on dogs followed essentially the methods previously described.[9] Oxygen containing 30 to 40 per cent carbon dioxide was administered through an endotracheal catheter from a nonrebreathing valve system. Observations included arterial blood pH, electrocardiogram, hematocrit, blood pressure, plasma volume, and plasma and red blood cell electrolyte concentrations.

RESULTS

Experiments on Rats.—Concentrations of carbon dioxide exceeding 50 per cent proved rapidly fatal due to respiratory failure. These rats were discarded. Most animals survived exposure to 35 to 45 per cent carbon dioxide for periods up to four and one-half hours. Nine of forty-six rats, however, died in the chamber after periods of one hour or more. In addition, a number of rats survived the period of hypercapnia but succumbed very suddenly after exposure to room air. The remainder were observed for a few minutes after removal from the chamber and were then sacrificed.

Electrolyte changes: In order to tabulate the results of the electrolyte determinations, the animals have been separated according to death or survival during hypercapnia and to duration of the hypercapnia in the latter group (Table I). The significant points are:

(a) The increasing value of plasma potassium with time accompanied by little change in the sodium or chloride concentrations. Particularly high values are noted in the animals dying in the chamber.

(b) The marked accumulation of intracellular potassium in the hearts of animals dying in the chamber and slightly increased potassium content of the hearts of animals dying or sacrificed shortly following return to room air. The water content of the hearts varied directly with the potassium content, as evidenced by a decrease in the percentage of solid weight when the potassium was increased.

TABLE I. COMPOSITION OF PLASMA AND HEART MUSCLE OF RATS BREATHING 35 TO 45 PER CENT CO_2

DURATION OF HYPERCAPNIA (HOURS)	NO. OF RATS IN GROUP	PLASMA			HEART MUSCLE		
		SODIUM MEQ./L.	POTASSIUM MEQ./L.	CHLORIDE MEQ./L.	% SOLIDS	SODIUM*	POTASSIUM*
Controls on air	14	151	4.63	109	23.9	214	387
		±1.88†	±0.12	±1.0	±0.27	±15.2	±6.3
1.5-2.4	19	148	9.68	106	23.3	203	398
		±2.0	±0.58	±4.0	±0.15	±6.5	±7.5
2.5-3.4	13	152	10.3	107	23.2	212	417
		±4.4	±0.73	±1.5	±0.24	±11.5	±7.8
3.5-4.4	5	160	11.0	103	22.2	227	417
		±3.6	±0.85	±2.3	±0.27	±11.1	±14.3
Died in chamber after 1 hr.	9	160	14.1		21.4	202	478
		±4.8	±0.76		±0.58	±4.7	±18.3

*Milliequivalents per kilogram of dry defatted tissue.
†Standard error of mean.

There were no significant changes in tissue potassium in liver, skeletal muscle, and kidney during hypercapnia. In the group dying in the chamber, there was an accumulation of liver sodium and chloride with an increase in tissue water. This may indicate a more gradual cardiac failure rather than acute cardiac arrest or fibrillation.

Electrocardiographic observations: There were no significant alterations in the electrocardiograms of the majority of animals during exposure to carbon dioxide. Animals dying in the hypercapneic period showed bradycardia followed by a prolongation of the QRS complex. Dropped beats then occurred and finally a complete atrioventricular block with ventricular arrest.

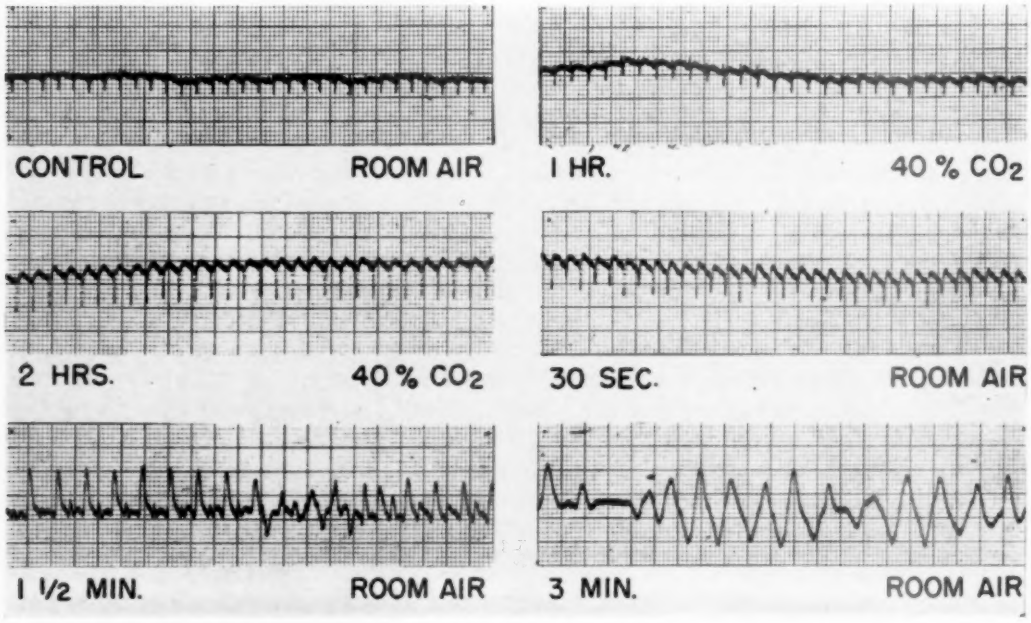

Fig. 1.—Rat BF. Electrocardiogram (Lead II) of a rat subjected to 40 per cent carbon dioxide in oxygen for two hours.

Of special interest was the occurrence of severe disturbances leading to fatal ventricular fibrillation in several of the animals shortly after return to room air. These changes are exemplified in Figs. 1 and 2. There was an increase in intraventricular conduction time as shown by a prolonged QRS complex. A definite T wave often appeared, and changes frequently occurred in the height and direction of the QRS complex. Ventricular extrasystoles and bursts of paroxysmal ventricular tachycardia occurred and seemed to presage fibrillation or widespread disorganization of the electrocardiographic tracing prior to death. Occasionally some animals showed minor electrocardiographic changes during hypercapnia. These animals seemed more likely to develop serious and fatal abnormalities after return to room air (Fig. 3).

Dog Experiments.—In order to evaluate the relationship between potassium and the rapidly changing electrocardiographic alterations, an animal larger than the rat had to be used since it was impossible to obtain serial plasma potassium determinations during the experiment in this animal. Dogs were selected since Brown and Miller[11, 14] have already described posthypercapneic electrocardiographic phenomena in these animals which are similar to those noted here in the rat.

Dogs tolerated concentrations of 30 to 40 per cent carbon dioxide in oxygen for several hours. On this mixture, the blood pH fell usually to between 6.6 and 6.8. As in the rats, the most striking electrocardiographic abnormality was the occurrence of severe alterations, including ventricular fibrillation, in the posthypercapneic period despite relatively normal electrocardiograms obtained during hypercapnia (Fig. 4).

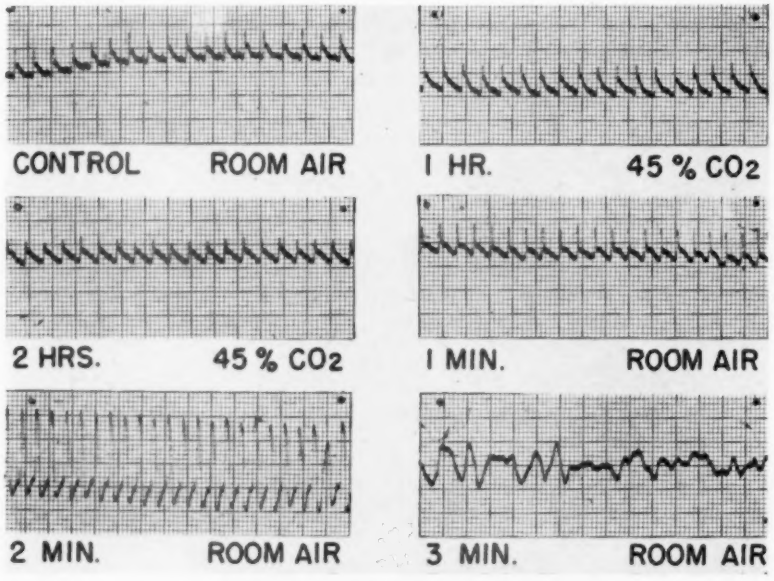

Fig. 2.—Rat AO. Electrocardiogram (Lead II) of a rat subjected to 45 per cent carbon dioxide in oxygen for two hours. The plasma potassium at death shortly after the last tracing was 12.8 meq. per liter.

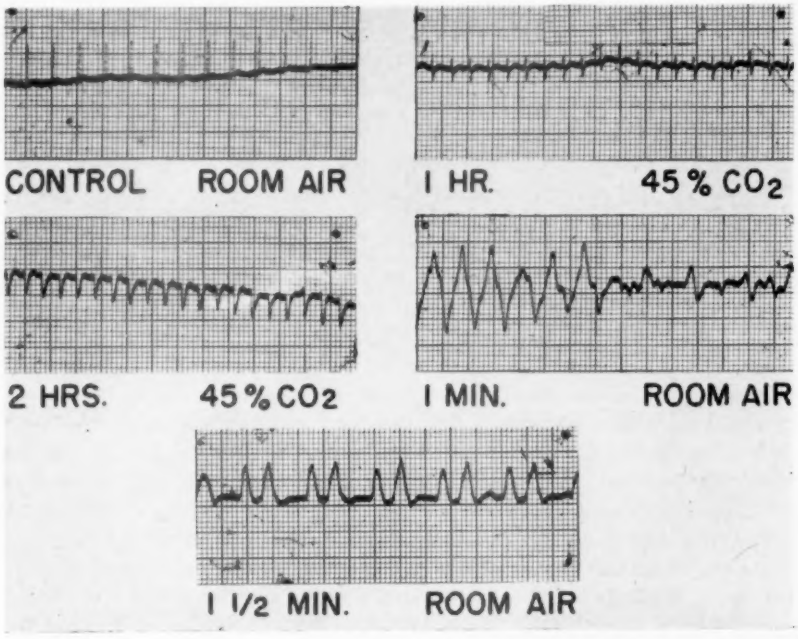

Fig. 3.—Rat AS. Electrocardiogram (Lead II) of a rat subjected to 45 per cent carbon dioxide in oxygen. Plasma potassium at death shortly after the last tracing was 13.9 meq. per liter.

Determinations of plasma potassium revealed a progressive rise in the potassium concentration during hypercapnia. When the animals were returned to room air or oxygen, there was a transient further increase in the potassium concentration which coincided with the period of maximal electrocardiographic abnormalities. A typical example is shown in Fig. 5, which depicts the alterations in the dog whose electrocardiogram is shown in Fig. 4.

In twenty-one dogs the average control plasma potassium concentration was 3.91 meq. per liter with a range of from 2.8 to 4.6. On 30 to 40 per cent carbon dioxide this rose to a level of 6.89 meq. per liter (range of 4.7 to 10.2), while in the immediate posthypercapneic period, an average maximal potassium concentration of 7.86 was reached (5.5 to 10.2). One of these dogs showed a potassium rise from 4.2 to 10.2 during the breathing of 35 per cent carbon dioxide. When changed to room air, the animal suddenly fibrillated and died before another blood sample could be taken.

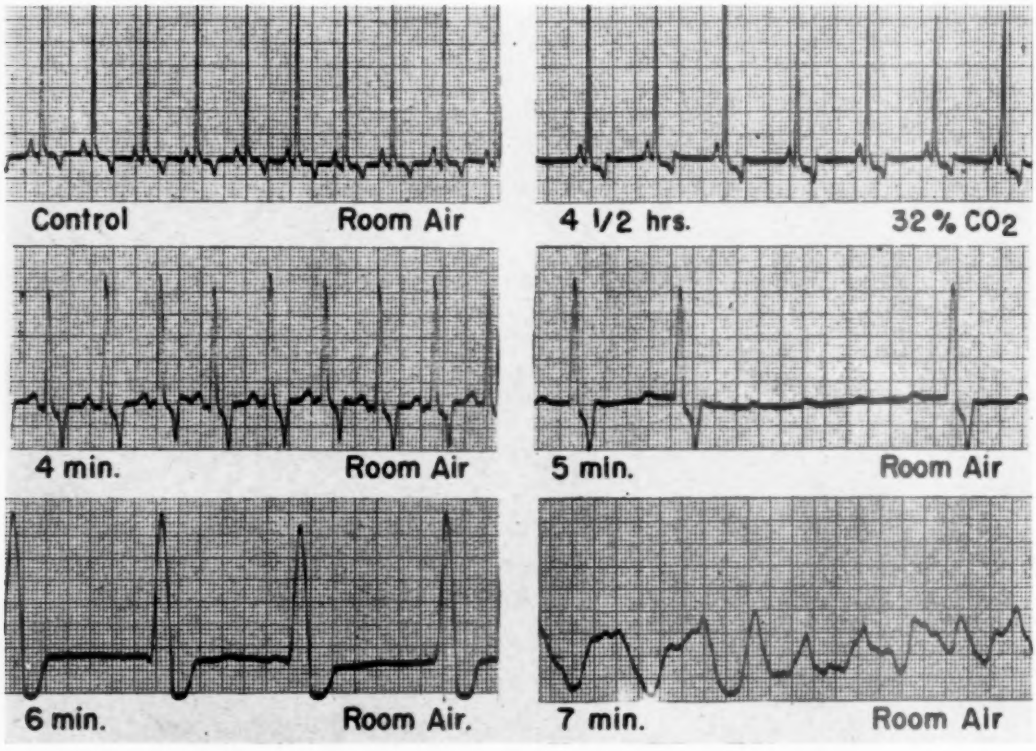

Fig. 4.—Dog 21c. Electrocardiogram (Lead II) of a dog subjected to 32 per cent carbon dioxide in oxygen. The changes in plasma potassium are shown in Fig. 5.

The relation between the plasma potassium levels and the electrocardiograms during and after hypercapnia is more clearly shown in Table II, where the animals have been divided into those showing no significant electrocardiographic changes and those showing moderate to marked alterations. The difference in the plasma potassium concentration in the groups is striking. During or immediately after breathing the carbon dioxide mixture, only three of the fourteen animals showing electrocardiographic changes had plasma potassium levels less than the highest shown by the group without electrocardiographic alterations.

The hematocrit generally increased when the animal was placed on carbon dioxide mixtures—a finding probably related to splenic contraction. In gen-

TABLE II. RESULTS IN TWENTY-ONE DOGS SHOWING THE RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC ABNORMALITIES AND PLASMA POTASSIUM CONCENTRATIONS (MILLIEQUIVALENTS PER LITER) DURING AND AFTER HYPERCAPNIA

	NO. OF DOGS	CONTROL POTASSIUM	PLASMA POTASSIUM ON CO_2	PLASMA POTASSIUM POST-CO_2
Entire group	21	3.91 (2.8-4.6)	6.89 (4.7-10.2)	7.86 (5.5-10.2)
Group with electrocardiogram changes	14	3.90 (2.8-4.3)	7.46 (5.5-10.2)	8.52 (6.6-10.2)
Group without electrocardiogram changes	7	3.94 (3.1-4.6)	5.73 (4.7-6.4)	6.63 (5.5-7.9)

eral, the plasma sodium, plasma chloride, and red blood cell potassium concentrations remained relatively constant both during and immediately after hypercapnia (for example, Fig. 5).

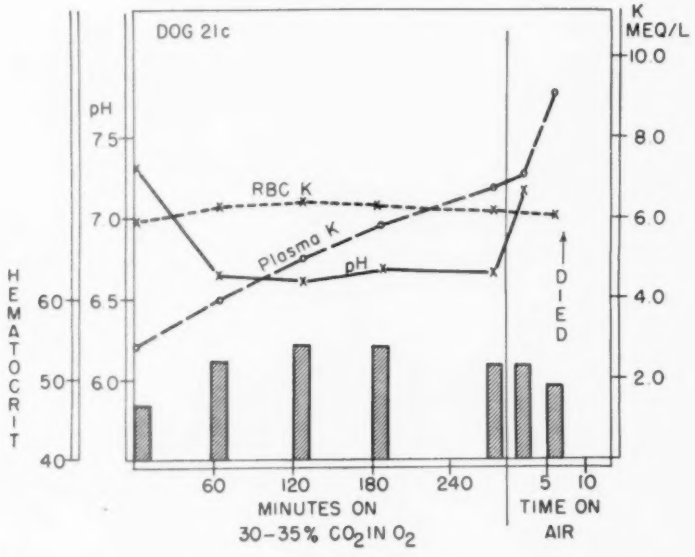

Fig. 5.—Blood studies on dog whose electrocardiogram is shown in Fig. 4.

Figs. 6, 7, 8, and 9 show attempts to alter the electrocardiograms and potassium concentration by means of hypertonic saline solution and glucose. As is seen, there was marked improvement in the electrocardiographic alterations concomitant with a decrease in potassium concentration. At the same time, the drop in hematocrit and fall in plasma proteins indicated an expansion in plasma volume. In other experiments where fibrillation had already occurred, attempts to revert the rhythm to normal by means of intravenous therapy were unsuccessful, probably because circulation had already stopped.

DISCUSSION

The results in rats and dogs show that there are pronounced changes in potassium metabolism during and immediately following acute hypercapnia. These changes may be correlated with electrocardiographic abnormalities which resemble those of hyperpotassemia.

The changes in the plasma potassium concentrations confirm and extend the results of Mackay,[15] who found a transitory rise in serum potassium of cats (from 2.9 to 8.3 meq. per liter) during the first thirty minutes of exposure to 35 per cent carbon dioxide. Similar findings of a rise in serum potassium are well known in asphyxia, where anoxia and release of adrenaline may also be important factors.[16] Mackay[15] found that adrenalectomy did not prevent the rise in potassium during hypercapnia but that evisceration abolished it. Similar findings have been reported by Houssay and co-workers[17] in asphyxia in dogs. Our analytic data do not localize the origin of the excess potassium. This failure is not unexpected since the amounts making up the rise in the plasma are but a small fraction of the large stores in either the liver, muscle, or bones. In contrast to skeletal muscle, the heart shows a definite increase in potassium concentration. The nature and significance of this difference in metabolism are unknown.

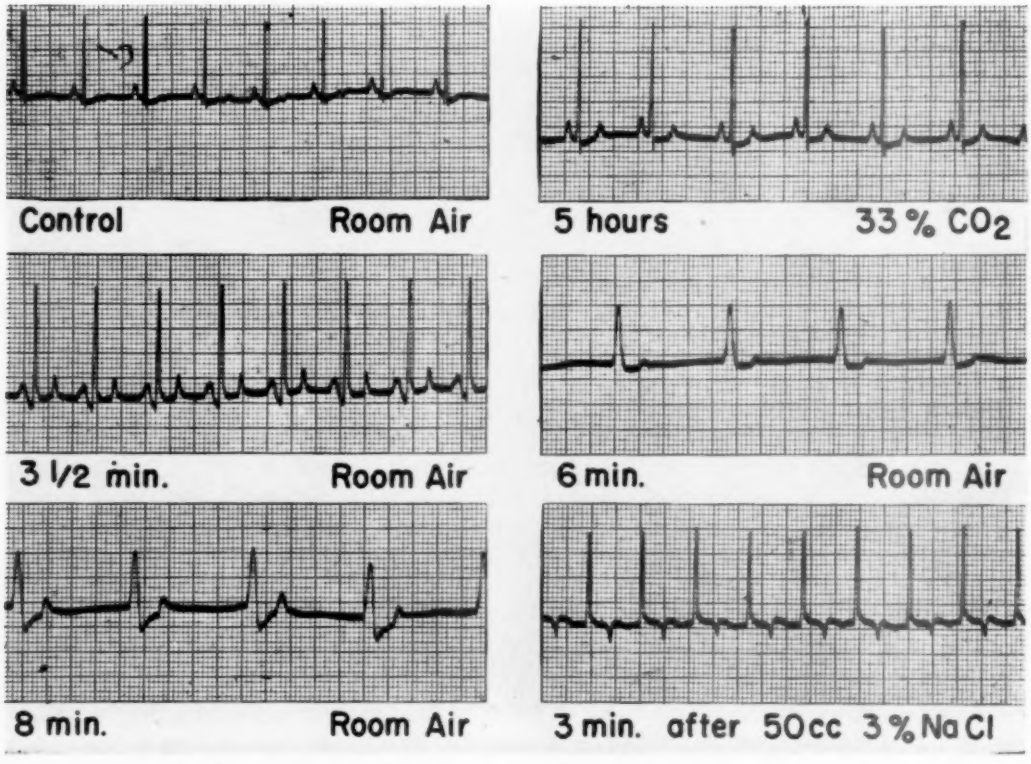

Fig. 6.—Dog 23c. Electrocardiogram (Lead II) of a dog subjected to hypercapnia and given hypertonic saline solution in posthypercapneic period. Changes in plasma potassium are shown in Fig. 7.

The sudden further rise in plasma potassium concentration in the immediate posthypercapneic period is a striking and interesting finding. It is not known why, or how, this rise occurs, but speculation and present experimentation involve the possible roles of adrenal discharge, rapid changes in extracellular pH, and changes in cardiac muscle potassium.

Although minor changes in the electrocardiogram occur during hypercapnia, the major alterations appear in the immediate posthypercapneic period in both the rat and dog. The changes include bradycardia, auriculoventricular block, disappearance of P waves, alterations in height and direction of QRS and T waves, broadening of the QRS complex, ventricular extrasystoles, ventricular tachycardia, fibrillation, and arrest. Of clinical importance may be the observation that widening of the QRS complex precedes fibrillation or arrest by several minutes in almost every instance.

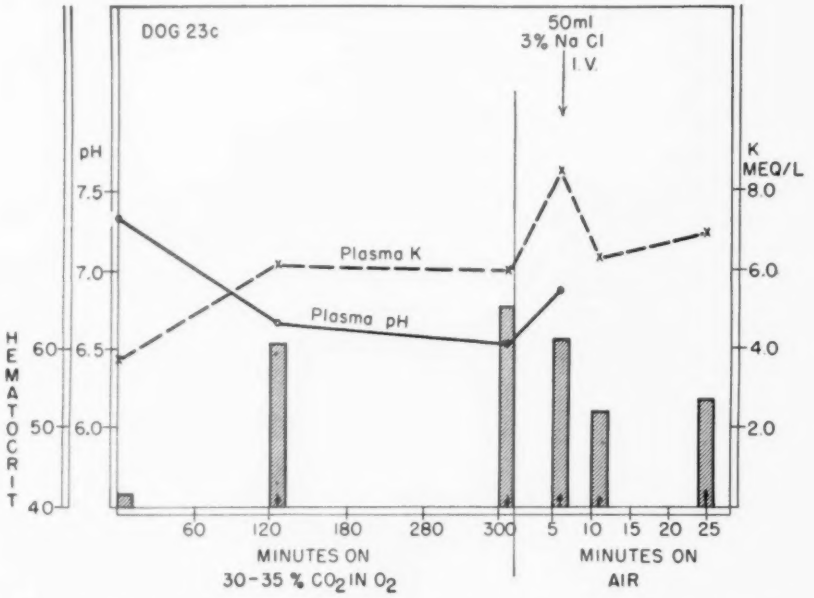

Fig. 7.—Blood studies on the dog whose electrocardiogram is shown in Fig. 6.

A causal relationship between the electrolyte changes and alterations in the electrocardiograms is suggested by those data. As Miller and associates[11] have already noted, the posthypercapneic electrocardiogram bears a remarkable resemblance to that occurring in potassium intoxication. Previously, Abrams, Lewis, and Bellet[18] noted a similar resemblance in the electrocardiograms of dogs made acidotic by the oral administration of ammonium chloride. They found a simultaneous rise in serum potassium and suggested that the electrocardiographic abnormalities were due to changes in the plasma potassium concentration, even though the average maximal rise was but 17 per cent over the control. Our data show a more striking rise in plasma potassium concentration during and immediately after hypercapnia, the extent of which varies in different species. The most severe electrocardiographic abnormalities occur at the highest potassium levels.

We believe that the two phenomena are causally related, although many other factors may play roles. These factors include (a) the effect of prolonged respiratory acidosis and the rapidly shifting pH during the posthypercapneic

period on the sensitivity of the heart to potassium intoxication, (b) the effect of alterations in blood pressure and coronary flow, (c) the effect of changes in vagal tone, and (d) possible effects due to changes in other electrolytes.

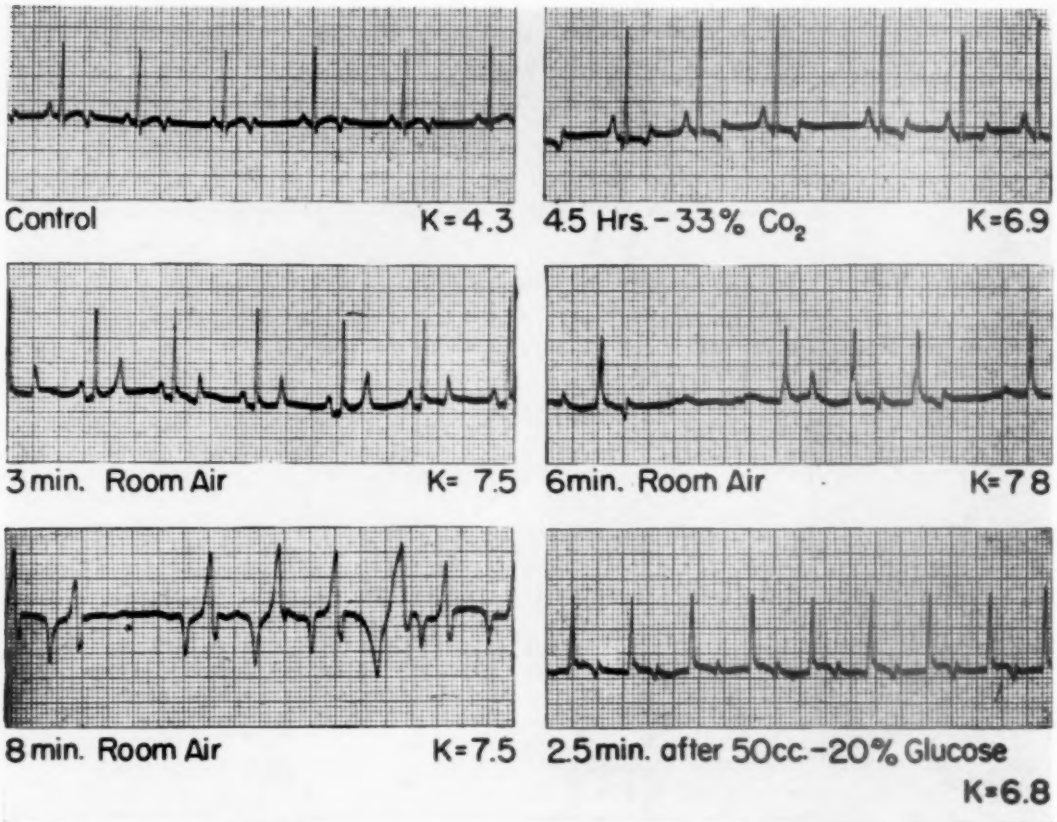

Fig. 8.—Dog 35c. Electrocardiogram (Lead II) of a dog treated with hypertonic glucose solution during the posthypercapneic period. K refers to plasma potassium concentration in milliequivalents per liter.

There are many indications that changes in acid-base balance may modify the effects of alterations in potassium metabolism. In unpublished experiments, we have found that anesthetized dogs, maintained with moderately high plasma potassium concentrations by an intravenous drip of potassium chloride, suddenly show pronounced evidences of potassium intoxication when given 30 to 40 per cent carbon dioxide to breathe. This occurred before there were marked increases in plasma potassium. Keating and his co-workers[6] found that potassium was much more toxic in dogs made acidotic with ammonium chloride. On the other hand, Black[19] has speculated on an increase in the symptoms of potassium deficiency during acidosis, an effect not expected from the previously discussed experiments on acidosis and potassium excess. Undoubtedly, acidosis causes many changes in cell metabolism and intracellular electrolytes which can alter the manifestations of variations in serum potassium. Perhaps the sudden appearance of electrocardiographic changes in the posthypercapneic period in our animals is caused not only by the further rise

in serum potassium but also by an altered sensitivity of the heart to potassium as a result of changes in cell physiology during the very rapid rise in extracellular pH.

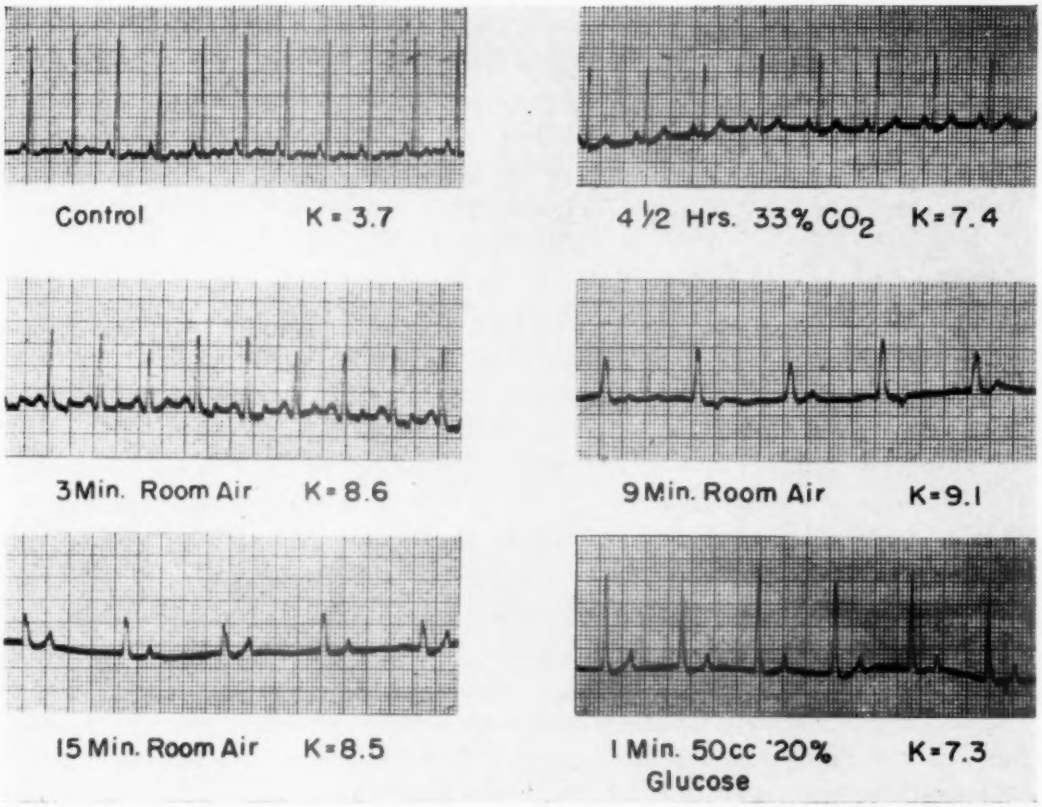

Fig. 9.—Dog 36c. Electrocardiogram (Lead II) of a dog treated with hypertonic glucose solution during the posthypercapneic period. K refers to plasma potassium concentration in milliequivalents per liter.

Another modifying factor may be the alteration in blood pressure and cardiac efficiency during respiratory acidosis. Although hypercapnia probably diminishes the contractile force of the heart in situ,[20] we and others[8, 11] have found that an elevation of blood pressure occurs when the respiratory mixture is changed from room air to high concentrations of carbon dioxide. In our experience this rise is transient and the blood pressure gradually returns to normal. In the immediate posthypercapneic period, there is a moderate fall in blood pressure. If the animal survives, the blood pressure returns to normal. In those animals showing pronounced and serious electrocardiographic changes, the blood pressure continues to fall until death. With Miller and associates,[11] we were unable to determine whether the fall in blood pressure was caused by failure of the myocardium or by peripheral vascular collapse. We do not believe, however, that the drop in blood pressure was sufficiently marked to be a primary factor in the electrocardiographic changes, although it may have been a contributory factor and of clinical importance.

Alterations in vagal tone and in the sensitivity of the heart to vagal stimulation may play a role. It is known that hypercapnia increases the effects of vagal stimulation on the heart.[9] This occurs prior to a rise in serum potassium. In addition, Hoff and co-workers[21] have shown that the sensitivity of the heart to vagal stimulation is increased in hyperpotassemia. These alterations are under investigation using blocking agents such as atropine.

Finally, the role of changes in other electrolytes remains to be clarified. Serum sodium, chloride, and, in a few experiments, calcium were not significantly altered. Unpublished experiments of Davis and Welt[22] have shown an increase in blood glucose and phosphate—a finding which might implicate the liver as the source of potassium since it is well known that potassium, glycogen, and phosphate are associated in liver carbohydrate metabolism.

The effectiveness of hypertonic sodium chloride and glucose in temporarily correcting the electrocardiographic abnormalities due to hyperpotassemia in uremia was demonstrated by Finch[23] and others. In our studies these two agents have been equally effective in preventing fatal cardiac arrhythmias in the posthypercapneic dog. Whether this is because of a specific action of salt and glucose on potassium metabolism or whether the effect is secondary to nonspecific changes such as increase in blood volume or pressure is as yet unknown.

The clinical implications of this study are obvious. In human beings undergoing surgery, many more nonspecific factors may play a role—nutrition, infection, blood loss, hypothermia,[24] potassium administration with transfusions, anesthetic agents, and vasopressor drugs. Of special significance in our study is the regular appearance of QRS prolongation as a herald of more serious disturbances. It is suggested that continuous electrocardiographic observation be maintained during prolonged surgery to warn of impending arrest or fibrillation. If prolongation of the QRS complex occurs, treatment with hypertonic glucose or saline solution may be indicated on the basis of these studies.

SUMMARY

The effects of acute prolonged hypercapnia on electrolyte metabolism and the electrocardiogram were investigated in dogs and rats. When breathing 30 to 45 per cent carbon dioxide, these animals showed a progressive rise in plasma potassium concentration. In the immediate posthypercapneic period there was an additional sharp increase in the plasma potassium level. At the same time, serious electrocardiographic disturbances frequently appeared and terminated in ventricular fibrillation or arrest. The hypothesis is advanced that the rise in plasma potassium concentration is the primary cause of the electrocardiographic abnormalities, although secondary and less specific factors may play roles. Hypertonic glucose and saline solution have been found to be effective in reversing the electrocardiographic changes if given sufficiently early. The implications of these findings in human cardiac arrest occurring during surgery are discussed.

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DISCUSSION

DR. HENRY SWAN (Denver, Colo.).—I certainly would like to congratulate Dr. Young and his group on their work. It is terribly important because he is getting additional evidence on the relationship between potassium and cardiac irregularity. This, if carried further, may lead to some very practical methods of prevention and control of

cardiac arrest in all types of surgical situations. I hope that in the course of time we will be able to accumulate some knowledge as to why potassium goes in and out of cells and, specifically, why it goes in and out of the myocardial cell, and from there what the significance is on heart function.

Now, I am sure we all agree that there is some relationship between the distribution of potassium in the body and the tendency of the heart to undergo irregularities. Thus, hypercapnia causes a change in the serum potassium, as was so beautifully demonstrated here. The opposite is also true. If one overbreathes the animal, the K changes go in exactly the opposite direction. There appears to be a reciprocal relationship between pH and serum potassium.

In regard to fibrillation itself, we know of at least two specific relationships between ventricular fibrillation and potassium. We have recently been studying the electrolyte pattern of coronary blood following regular fibrillation. In the presence of ventricular fibrillation, there is an extraordinary outpouring of large volumes of potassium into the coronary blood. In addition to this we know that if you perfuse the coronary system with potassium chloride of a heart in ventricular fibrillation, it will stop the fibrillation. We have found that there may be a relationship between acetylcholine and the cholinesterases and this distribution of potassium in the heart. If one gives acetylcholine or one of the anticholinesterases, such as Prostigmine, one finds a very pronounced change in, first, the tendency of this heart to fibrillate when certain stimuli are applied and, second, a very definite change in the disposition of the potassium. Our data at the present time are incomplete on this, but they do corroborate Dr. Young, on this very important point that he is working on. Understanding of where the potassium is and why it goes there will, I am sure, be a very important addition to our knowledge on the subject of cardiac irregularities.

DR. HERBERT C. MAIER (New York, N. Y.).—I think this work by Dr. Young and Dr. Sealy explains well the clinical observation that the time when the carbon dioxide accumulation is decreasing at the end of an operation may be the time when an unexplained cardiac arrest may occur.

As you noted, the authors were dealing with concentrations around 35 per cent CO_2 in the inspired gas in their experimental animals. That may seem like a very excessive amount to you, but it is startling to note that when examining patients undergoing surgical procedures in which, because of the anesthesia technique employed, the ventilatory motion is minimal, you can occasionally have concentrations of 20 or 25 per cent carbon dioxide in the gases in the airway. Moreover, you can get rapid pH changes with a drop down to 7.1 in as short a time as ten or fifteen minutes after a face mask is applied if the ventilation is markedly reduced. Yet that degree of ventilation may be entirely adequate for full oxygenation. Similar situations definitely do occur clinically. I think we have to bear in mind also that other factors such as the use of citrated blood and changes due to hemorrhage itself aggravate the physiologic disturbances from the carbon dioxide accumulation.

DR. HENRY THOMAS RANDALL (New York, N. Y.).—What happened to the oxygen saturation in these animals on removal from their high CO_2 environment? We have some experimental work under way in our laboratory which seems to suggest that the potassium level changes and the electrocardiographic changes which go along with them do not occur to such a degree unless there is also a sharp decrease in oxygen tension. I wondered what happened to the respiratory rate and volume of these animals and whether or not Dr. Young made oxygen saturations during this acute period following removal from the high CO_2 environment.

DR. SEALY (Closing).—Gentlemen, we appreciate the remarks of Dr. Swan and Dr. Maier. In answer to Dr. Randall's question, we do not believe anoxia plays a role in the posthypercapneic potassium rise. This change occurs with the animals breathing

100 per cent oxygen and with the respiratory rate increased greatly. There is drop in the blood pressure in this period, but this is usually of the range from 100 mm. Hg to 80 mm. Hg mean.

Cardiac arrest now constitutes one of the major causes of death from surgery. Carbon dioxide retention has been implicated as a cause of this accident, although its exact mode of action was not understood. In fact, one of the striking observations in these experiments was how well the animals tolerated large amounts of carbon dioxide with very little alteration in the blood pressure or electrocardiogram. The observation that the critical time in the experiments was after the carbon dioxide was stopped fits in well with our study of patients who died from cardiac arrest. Nearly one-third of the cases occurred at the end of an abdominal operation when the patient was being hyperventilated. Preceding the period of hyperventilation, the patient's anesthetic level was usually deepened. It is very tempting to speculate about the relationship of this clinical finding to our laboratory observations.

PULMONARY EMBOLISM: A CLINICAL STUDY OF NINETY-SEVEN FATAL CASES

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PULMONARY embolism is one of the few conditions whose incidence and mortality have not been significantly reduced by improved knowledge and increased attention to the problem. According to Barnes,[7] about 34,000 people die annually of pulmonary embolism, a figure which seems to be increasing. We have, therefore, re-examined our records to verify these statements and to determine where we might improve our methods of diagnosis and care of such patients.

Pulmonary embolism in clinical practice is usually the result of occlusion of the pulmonary arterial tree by embolization of a blood clot which has originated in the vena caval system or in the right heart. For purposes of this paper, gaseous emboli obstructing the pulmonary arterial tree and in situ thrombosis of the pulmonary artery will not be considered. Since each embolus is first a thrombus, it is evident that much of our failure to deal adequately with the problem of embolus can be traced to our inadequate information about and control of the factors which predispose toward intravascular clotting and, to a lesser extent, to the factors which actually cause this clot to break loose to become an embolus. Because of the notorious inaccuracies to which the diagnosis of both thrombosis and embolus are subject, our study has been limited solely to patients who have been proved at autopsy to have died of pulmonary embolism.

SOURCE OF MATERIAL

Our material is drawn from a private general hospital of 375 beds and seventy-five bassinets during the period 1930-1953. During this period there were 161,116 admissions and 6,609 deaths, autopsies being performed in 2,457 or 37 per cent of all deaths. During this period there were 97 deaths shown by autopsy to have been caused by pulmonary emboli. When the incidence of emboli was compared with the number of total hospital admissions by five-year periods, it was noted that there had been an almost steady increase in the incidence of fatalities from this cause. Death due to pulmonary embolus occurred in 0.045 per cent of patients admitted to the hospital during 1930-1935, but during the period 1950-1953, this incidence had increased to 0.089 per cent (see Table I). The over-all mortality due to pulmonary embolus during the period 1930-1953 was 0.054 per cent of admissions. Oehsner and associates,[22] in a similar series of 647,650 hospital admissions, encountered 383 deaths due to pulmonary embolism, an incidence of 0.059 per cent. Examination of our autopsy records (see Table II) shows that death due to pulmonary embolism has increased from 2.9 per cent during 1930-1935 to 5.0 per cent from 1950-1953.

Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

*1100 USAF Hospital.

This has been the experience of Anfus and Neuhof,[3] who in a series of 800 consecutive autopsies performed prior to 1930 found an incidence of fatal pulmonary emboli of only 3 per cent, whereas in a similar series performed during 1938-1947 the incidence had risen to 8.3 per cent. Miller and Berry[20] have reported an incidence of 5 per cent and McCarthy[18] an incidence of nonfatal pulmonary emboli of 10 per cent and 3 per cent fatal emboli.

TABLE I. INCIDENCE OF PROVED FATAL PULMONARY EMBOLI IN 161,116 HOSPITAL ADMISSIONS 1930-1953

YEARS	HOSPITAL ADMISSIONS	PROVED DEATHS DUE TO EMBOLI	% INCIDENCE
1930-1935	17,239	8	0.0458
1935-1940	26,981	11	0.0407
1940-1945	37,259	15	0.0403
1945-1950	46,204	33	0.0701
1950-1953	33,433	30	0.0890
Total	161,116	97	0.0540

TABLE II. AUTOPSY INCIDENCE OF PULMONARY EMBOLUS 1930-1953

YEARS	NO. OF AUTOPSIES	NO. OF PULMONARY EMBOLI	% INCIDENCE
1930-1935	273	8	2.9
1935-1940	355	11	3.1
1940-1945	459	15	3.2
1945-1950	775	33	4.2
1950-1953	595	30	5.0
Total	2,457	97	3.9

The incidence of pulmonary embolism as related to the various hospital services is revealed in Table III. Fatal pulmonary emboli are most common on the medical services, where pulmonary emboli have been responsible for death in 0.133 per cent of all medical admissions. This figure is likewise comparable to the 0.174 per cent reported by Ochsner. The surgical service by contrast had an incidence of fatal pulmonary emboli of only 0.027 per cent, less than one-quarter of that encountered on the medical service despite the fact that the gynecologic service had a patient incidence of 0.050 per cent and the urologic service an incidence of 0.039 per cent. This relatively higher incidence of pulmonary embolism encountered on the gynecologic service has often been attributed to postabortive and other pelvic inflammatory conditions. However, although we have recorded a high incidence of fatal pulmonary emboli on the gynecologic service, it could not be correlated with pelvic inflammation in any of our fatal cases. It would appear, therefore, that although pelvic inflammatory disease does undoubtedly predispose toward thrombosis, it is less likely to result in pulmonary emboli than the thrombi which originate at the site of surgical ligation of the pelvic vessels or sites of damage to these vessels incident to surgery. This same explanation would seem to be applicable to the fatalities on the urologic service although perhaps even more important is the frequent association of cardiac disease and relative immobility of the patients whose age in a majority of instances causes them to require this type of surgical care. Robertson,[23] in a survey of 2,196,834 operated cases, encountered deaths due to pulmonary emboli in 0.27 per cent of all cases, Barker,[4] at Mayo Clinic, in 158,000 cases reported an incidence of 0.22 per cent, and Donaldson[13] reported an incidence of approximately 0.1 per cent. Deaths due to pulmonary embolism, then, are relatively infrequent on a surgical service. Wenzl and Kühlmayer,[26]

in a survey of the problem of embolism at the Vienna surgical clinic over a sixteen-year period, have been unable to show that embolism in surgical patients has increased significantly. Hence, the increasing incidence of pulmonary embolism has been mainly in the gynecologic service. Table IV shows that the incidence of embolism on our surgical service, exclusive of gynecologic surgery, has not been increasing.

TABLE III. INCIDENCE OF 97 FATAL PULMONARY EMBOLI BY SERVICE

SERVICE AND PROCEDURE	NO. OF DEATHS	NO. OF PATIENTS TREATED	% MORTALITY
Medicine	69	43,526	0.133
Gynecology			
Hysterectomy and/or oophorectomy	6	11,880	0.050
Dilatation and currettage			
Genitourinary surgery			
Suprapubic prostectomy	3	7,553	0.039
Transurethral prostatectomy			
Cystoscopy			
Orthopedics and fractures			
Amputation	5	13,778	0.036
Pelvic fracture			
Fracture reduction			
Shoulder reconstruction			
Hip pinning			
General Surgery			
Gastric resection	13	48,415	0.027
Colon surgery			
Cholecystectomy			
Radical mastectomy			
Hernia			
Appendectomy			
Severe contusion			
Obstetrics	1	35,964	0.0027
Total or mean	97	161,116	0.054

TABLE IV. INCIDENCE OF PULMONARY EMBOLUS ON THE SURGICAL SERVICE EXCLUSIVE OF GYNECOLOGIC SURGERY 1930-1953

YEARS	ALL SURGERY EXCEPT GYNECOLOGIC (%)
1930-1935	0.030
1935-1940	0.020
1940-1945	0.032
1945-1950	0.032
1950-1953	0.022
Total	0.027

The rarity of fatal pulmonary emboli during pregnancy is well known and was confirmed by our data, our incidence being 0.0027 per cent of all obstetrical admissions. It must be admitted that infected abortions and post-partum infections are a great rarity in our experience, and special precautions are usually taken to eliminate or control varicosities in the majority of instances. Nevertheless, it is difficult to explain this low mortality rate in view of the known venous stasis in the pelvis and lower extremities during pregnancy unless it be assumed that pulmonary emboli do occur from these sources but are small and readily compensated for by a patient whose bodily physiology in this age group is usually excellent. That such infarcts may occur and go on to spontaneous

recovery, if the vascular system is otherwise normal, has been demonstrated experimentally by Chapman and co-workers.[10] Our inaccuracy in diagnosis of pulmonary embolus also favors this explanation.

ANALYSIS OF FACTORS PREDISPOSING TOWARD THROMBOSIS AND EMBOLIZATION

To reduce future fatalities caused by pulmonary emboli, we must be aware of the factors which predispose toward thrombus formation and embolization. Miller and Berry[20] have speculated that the increasing average age of the population and the increasing incidence of surgical and accidental trauma are responsible for the increasing frequency of death due to pulmonary emboli. However, increasing age per se is neither a specific nor a useful explanation, and since persons whose deaths are associated with trauma are usually unavailable for study (coroner's cases), we must look elsewhere for our answers. Age and its accompanying specific diseases do definitely predispose toward pulmonary embolism since, as Table V illustrates, 81 per cent of our fatal cases occurred in the age group over 40 years of age, the median being the group 60-70. All writers in the field agree on this point.

TABLE V. AGE INCIDENCE IN 97 FATAL CASES OF PULMONARY EMBOLISM

AGE (YR.)	NO. OF CASES	% INCIDENCE	
0-10	0	0	
11-21	3	3.1	18.6
21-30	6	6.2	
31-40	9	9.3	
41-50	12	12.3	
51-60	23	23.7	
61-70	27	27.8	81.4
71-80	13	13.4	
81-90	4	4.1	
91-100	0	0	
Total	97	100	

Of these patients, 30.9 per cent had had previous pulmonary emboli and 11.9 per cent had had more than one previous embolus.

It has been reported by Ochsner[22] that fatal pulmonary emboli are twice as common in males as in females, but the reports of Wenzl and Kühlmayer,[26] Zimmerman,[28] and our own statistics, which show a preponderance of females (54.5 per cent), disagree. Since most autopsy series do not demonstrate any clear-cut preference of pulmonary emboli for either sex, it can hardly be a predisposing factor of importance.

The specific disease states or conditions of physiologic imbalance which predispose toward intravascular clotting and embolization are worthy of more attention. De Takats[11] has stated that "it has been customary since the teachings of the older pathologists to regard slowing of the circulation, changes in the vessel wall, and increased coagulability of the blood as the three factors responsible for thrombosis." Table VI summarizes the occurrence of conditions related to these three factors in our fatal cases of pulmonary emboli. Since commonly more than one condition favoring thrombosis was present, and since it was often impossible to ascribe the primary responsibility to a single factor, the incidence of these conditions has simply been enumerated. Cardiovascular disease, immobilization, trauma, and dehydration appear to be the most important factors predisposing toward thrombosis.

Slowing of the Circulation—a Cardiac Disease.—Slowing of the circulation may be a local or generalized phenomenon and may occur in the heart, the peripheral circulation, or both, but it is evident that the heart occupies a special

position in this problem. The high incidence of fatal pulmonary emboli recorded on the medical service, 0.133 per cent, has already been noted and is indicative of the close correlation of cardiovascular disease and pulmonary embolism. In 63 of our 97 cases, 64.7 per cent, severe cardiac disease was present. According to Oehsner,[22] heart disease is associated with a higher incidence of fatal pulmonary emboli than any other disease, 25 per cent in this series, and 41 per cent of the fatal pulmonary emboli occurred in this group. The heart itself was the source of the embolus in 38 of our 97 cases, 39.3 per cent (see Table VII). Similarly, Miller and Berry[20] reported the heart to be the embolic source in 25 per cent of their series.

TABLE VI. FACTORS RESPONSIBLE FOR THROMBOSIS OCCURRING IN 97 FATAL CASES OF PULMONARY EMBOLI

	NO. OF CASES
A. Factors Tending to Slow Circulation	
Immobility (bed rest)	65
Cardiac disease	63
Shock	14
Cerebrovascular accident	8
B. Factors Producing Changes in Vessel Walls	
Peripheral vascular disease	68
Severe trauma or surgery	31
C. Factors Tending to Increase Blood Coagulability	
Marked dehydration	63
Severe trauma or surgery	30
Wound infection	15
Carcinoma	10
Systemic disease	6
Blood dyscrasia	1

TABLE VII. SOURCE OF 97 FATAL PULMONARY EMBOLI

SOURCE	NO. OF CASES	PER CENT
Heart		
Right auricle Right ventricle Interventricular Septum	38	39.3
Abdominal pelvis		
A. Iliac B. Broad ligament C. Inferior vena cava D. Hypogastric vein E. Vesicle vein	26	26.6
Extremities		
Upper—deep Lower—superficial deep	20	20.6
Unknown	13	13.5
Total	97	100.0

Table VIII illustrates the type of cardiac disease which, in our experience, was most frequently associated with fatal pulmonary embolism. Arteriosclerosis was the most frequent offender, followed by rheumatic heart disease and coronary occlusion in almost equal frequency. Bunn[8] has stated that pulmonary embolism is the most frequently overlooked complication of heart disease and is often the first clue to the presence of a thrombus in the right heart chamber. He has also emphasized that mural thrombi in the right heart are by no means rare and

occur in conjunction with auricular fibrillation especially if associated with mitral stenosis. Occlusion of a large coronary vessel, infarction of the interventricular septum or right heart wall, and bacterial or verrucous endocarditis not uncommonly produce pulmonary emboli. That pulmonary embolism is not more commonly fatal in rheumatic heart disease again is due to the presence of adequate compensatory mechanisms in the young age group, which is particularly subject to this disease. Still, Miller[21] has reported that pulmonary embolism is the most common immediate cause of death in young patients with rheumatic heart disease associated with auricular fibrillation.

TABLE VIII. CARDIAC DISEASES ASSOCIATED WITH 63 FATAL PULMONARY EMBOLI

DIAGNOSIS	NO. OF CASES	PER CENT INCIDENCE
Arteriosclerotic heart disease	28	44.4
Rheumatic heart disease	13	20.6
Coronary occlusion	12	19.1
Hypertensive heart disease	5	7.9
Bacterial endocarditis	3	4.8
Cor pulmonale	2	3.2
Total	63	100.0

Of our 63 patients with some form of cardiac disease, 42 or 66.6 per cent were known to be fibrillating at the time their pulmonary embolism occurred. It is significant that in 13 of these 63 cases, 20.6 per cent, there has been a recent change in the cardiac rhythm as a result of the therapeutic use of digitalis in 8 cases, digitalis and quinidine in 2 cases, and quinidine alone in 3 cases. It is, of course, well known that the conversion of an irregular to a regular cardiac rhythm will not infrequently provoke the embolization of a pre-existing auricular, valvular, or mural thrombus. In our cases, embolization occurred most commonly on the day the rhythm changed, although not always (see Table IX).

TABLE IX. RELATIONSHIP OF CARDIAC RHYTHM CHANGE TO PULMONARY EMBOLUS IN 13 CASES IN WHICH THE EMBOLIC SOURCE WAS THE HEART

DURATION OF ALTERED RHYTHM BEFORE EMBOLUS (DAYS)	NO. OF CASES	PER CENT INCIDENCE
0-1	9	69.2
1-2	1	7.7
2-3	0	0.0
3-4	3	23.1
Total	13	100.0

The average duration of cardiac medication in 13 cases prior to embolus was 3.45 days.

In coronary occlusion, one would expect that the associated incidence of pulmonary emboli would be rather high were it not for the fact that a relatively small percentage of these occlusions affect the blood supply to the right heart or interventricular septum. Binder and Sbertoli,[6] in a recent survey of 300 consecutive cases of coronary occlusion in our hospital during the period from 1947 to 1951, were able to show that pulmonary embolism was an associated complication in only 1.33 per cent of their series.

It is obvious that in the final stages of congestive heart failure, pulmonary emboli commonly occur as a result of the generalized slowing down of the circulation, anoxia of the blood and containing vessels, and alteration in the blood constituents, so that even when the heart itself is not the source of emboli, it influences peripheral thrombus and embolus formation. Levinson and Griffith[17] have recorded an 8 per cent incidence of pulmonary emboli in congestive failure, which tends to confirm this statement.

Venous Thrombosis.—The recent literature has perhaps overemphasized the importance of venous thrombosis in relation to the problem of pulmonary embolism. McLachlin and Paterson[19] reported a series of 100 complete dissections of the veins of the pelvis and lower extremities. In this group, there was evidence of pulmonary emboli in fifty-six cases, in thirty-four there were grossly demonstrable thrombi present, and in 73 per cent of these cases the veins of the thighs and pelvic veins were the sources of the pulmonary emboli. It would appear that the veins of the lower extremities, therefore, are not so commonly the source of pulmonary emboli as they were once thought to be. Even though it has been shown by Hunter and associates[16] that thrombi can be found at autopsy in the calf veins of 60 per cent of all adults, in our experience, venous thrombosis was the cause in only 47.2 per cent of our fatal cases of pulmonary embolism. Of these 46 thrombi which became emboli, 26 arose in the abdomen or pelvis proper, 4 arose in the upper extremities, and 8 arose in the superficial or deep veins of the lower extremity, respectively. More complete dissections of the lower extremity might have shown the source of emboli in the 13 cases in which we were unable to implicate the heart or the veins of the abdomen, pelvis, or upper extremity. It is not reasonable to ascribe these 13 cases to primary pulmonary thrombosis since this condition must be of very rare occurrence, for even its existence has been doubted by Billings.[5] However, it is possible that an entire peripheral venous thrombus may become detached in toto from its supporting vessel wall in becoming an embolus, thus leaving little or no evidence of its site of origin. Were this the explanation of our undetected source of emboli in our 13 cases, it would have given us only a 60.7 per cent incidence of pulmonary emboli due to venous thrombosis, and of these, only 34.1 per cent would have arisen in the combined superficial and deep veins of the lower extremities. We, therefore, believe that Hunter,[16] who reported the veins of the lower extremity to be the source of pulmonary emboli in 45 per cent of cases, to be closer to the correct evaluation of this problem than Barnes,[7] who reported 91 per cent, or Miller and Berry,[20] who reported 61.2 per cent of all emboli arising from the veins of the extremities.

The marked disagreement which exists over the relative importance of venous thrombosis and its most dangerous sites in the problem of pulmonary embolism serves to emphasize our present difficulty in making a diagnosis of "silent" venous thromboses even in the presence of known nonfatal pulmonary emboli. Allen and co-workers[1] have stated that in only 15 per cent of 343 cases was there clinical evidence of thrombophlebitis prior to death from pulmonary embolism. Welch and Faxon,[25] in a study of 128 fatal cases of pulmonary embolism, found that 5.5 per cent had clinical evidence of peripheral venous disease prior to embolization. Likewise, Felder[14] has stated that in a group of twenty-eight fatal cases of pulmonary embolism, he encountered only seven patients who showed signs of phlebitis more than one day prior to embolization, and in ten these signs appeared only on the day of pulmonary embolic occlusion, while in the remaining eleven, the embolus was the first indication of venous thrombosis. Of our 46 cases where venous thrombosis could be shown at autopsy to have been the source of embolus, only 45.5 per cent demonstrated the well-known local signs of thrombophlebitis, that is, local pain, swelling of the area or extremity, redness, or locally increased temperature, or in fact showed even such nonspecific signs as increased body temperature or tachycardia (see Table X). The scarcity of detectable signs is, in part, accounted for by our previous observation that in 26 of our 46 cases, the site of venous thrombosis was in the pelvis. De Takats and Fowler[11] have described the less well-known signs and symptoms of pelvic vein thrombosis, but these are not always obvious and may not be appreciated in a patient who has been previously subjected to abdominal

or pelvic surgery. These symptoms may be pain and swelling in the buttocks or in the adductor muscles close to the inguinal fold, sciatic neuritis, frequency of urination, mucous diarrhea, and slight suprapubic edema, or palpable cords lateral to the prostate or uterus.

TABLE X. SYMPTOMS OF THROMBOSIS IN 46 CASES OF EMBOLISM OF NONCARDIAC ORIGIN

SYMPTOM		NO. OF CASES	PER CENT INCIDENCE
No symptoms		25	54.5
Local symptoms			
Pain	19		
Edema	14		
Heat	10		
Redness	5	21	45.5
Systemic symptoms			
Fever	13		
Tachycardia	10		
Total		46	100.0

In our 46 cases having origin of the thrombus outside the heart, the duration of thrombosis prior to embolus formation can be roughly estimated, since in 20 of these cases, 45.5 per cent, a clinical diagnosis of thrombosis was made prior to the occurrence of pulmonary embolization and in 19 cases the duration of the thrombus could be roughly estimated from the time of the probable precipitating factor, that is, surgery or other trauma. In the remaining 6 cases a diagnosis of thrombosis was not made prior to death, and the histories of these cases revealed no specific predisposing event from which probable thrombosis could be dated. Table XI summarizes our information in the remaining 41 cases and indicates that roughly one-half of all fatal pulmonary emboli occurred during the first six days following thrombosis and the remainder occurred in the succeeding three days. Allen, Barker, and Hines[2] have stated that "after a venous thrombus has existed in situ for three or four days at the most and has produced clinical signs and symptoms of thrombophlebitis, this thrombus does not detach to form an embolus," but it is clear that more recent proximal propagation of the original clot or new clots can and does frequently form emboli.

TABLE XI. DURATION OF PERIPHERAL THROMBOSIS TO TIME OF OCCURRENCE OF PULMONARY EMBOLISM IN 41 CASES

DURATION OF THROMBOSIS (DAYS)	NO. OF CASES	PER CENT INCIDENCE
0-1	2	4.9
1-3	6	14.6
3-6	9	22.0
6-9	24	58.5
Total	41	100.0

The actual activity which appeared to provoke detachment of the thrombus from its source was insignificant in 50 cases, 51.5 per cent, but in the remainder there was a history of increased activity or strain which appeared to be associated with the acute pulmonary insult (see Table XII).

Alterations in the Blood Composition Favoring Thrombosis.—It has long been accepted that abnormal increases occur in certain of the substances necessary to the clotting mechanism, on occasion. For example, surgery as well as trauma liberates thrombokinase, which increases the clotting tendency, although, as indicated by our previous discussion, this tendency only rarely results in un-

desirable degrees of thrombosis. This statement might also be said to apply to infection, which also increases the clotting tendency. Spontaneous thromboses also are said to be more prevalent in patients suffering from carcinoma as well as in certain blood dyscrasias, such as polycythemia. Since our hospital admits an average of 320 patients with carcinoma a year and we have encountered only 9 who succumbed to pulmonary embolism, and since we lost only one polycythemia patient from this cause out of approximately 21 who have been cared for over this twenty-three-year period, the degree to which these conditions predispose toward thrombosis and embolism must be slight in comparison with other factors favoring increased intravascular clotting.

TABLE XII. ACTIVITY ASSOCIATED WITH EMBOLIZATION OF THROMBUS IN 97 FATAL CASES OF PULMONARY EMBOLISM

ACTIVITY	NO. OF CASES	PER CENT INCIDENCE
None (that is, bed rest)	50	51.5
Ambulation	22	22.7
Nursing care	9	9.3
Sitting up	7	7.2
Straining at stool	3	3.1
Restlessness in bed	3	3.1
Instrumentation*	3	3.1
Total	97	100.0

*Of two patients with known venous thrombosis of the extremities, one developed a fatal embolus during cystoscopy and the other while undergoing uterine curettage. A third patient with no known thrombovascular abnormality developed a fatal embolism during urethral catheterization.

Since increases in certain of the elements necessary to blood clotting favor increased clotting activity, it might be expected that a relative increase in all the substances necessary for this activity, such as occurs with marked dehydration, would also increase intraluminal clotting. Clotting due to dehydration would be accentuated by so-called "sludge formation" due to loss of much of the blood's fluid component as well as by the accompanying reduction in blood pressure, peripheral oxygenation, and general bodily activity. De Takats and Fowler[11] were able to show such a decreased coagulation time by means of the heparin tolerance test in patients dehydrated by mercurial diuretics, while the factors favoring clotting just mentioned, that is, reduced oxygenation, decreased activity, and sludge formation, would accentuate this tendency. In 63 of our 97 fatal cases of pulmonary embolus there was definite evidence of dehydration prior to the occurrence of embolization. In 33 of these cases, dehydration was incidental to disease processes which had caused excessive fluid loss, such as vomiting, diarrhea, and duodenal fistulas, whereas in the remaining 30 cases, dehydration had recently been accomplished by means of mercurial diuretics, ammonium chloride combined with fluid restriction, or by means of digitalis where it was felt desirable to reduce fluid retention caused by cardiac decompensation (see Table XI). It is pertinent to the problem, we believe, to record that during the period 1930-1940, during which time mercurial diuretics were not employed at our hospital, there were only 11 deaths in 12,367 medical admissions, whereas during the period 1940-1953, when mercurial and other potent diuretics were being employed, in a total of 31,159 medical admissions there were 58 deaths due to pulmonary embolism, an incidence of 0.089 per cent in the first instance and 0.186 per cent in the latter (see Table XIII). This increased incidence of pulmonary embolism on the medical service, which has been paralleled by the increased use of mercurials, is an increase which is significantly greater than the over-all increasing incidence of embolism. To illus-

trate the type of case which suggested to us the close relationship of dehydration to pulmonary embolism, we cite the following case history:

A 61-year-old white man was admitted to St. Francis Hospital suffering from arteriosclerotic heart disease which had caused auricular fibrillation and cardiac decompensation. Because this patient while at home had failed to respond satisfactorily to digitalis and had remained edematous, he was placed on a restricted fluid intake and was given 3 Gm. of ammonium chloride by mouth daily together with 2 c.c. of Salyrgan every other day. During the first two days of treatment, the patient's average urinary output exceeded by 1,695 c.c. his oral intake. During the following twelve days, urinary output exceeded oral intake by 200 c.c. daily on the average. At the end of this two-week period, and in the absence of any previous indication of cardiac or peripheral thromboses, the patient developed severe precordial pain, which radiated to the left arm. The patient at this time was believed to have had an acute coronary arterial occlusion. Further dehydration therapy was discontinued, but one week later the patient complained of discomfort in the left lower abdomen and groin without other associated complaints or findings. Despite the absence of clinical findings, venous thrombosis of the left iliac vein was suspected. Forty-eight hours later, the patient noted pain, cyanosis, and edema of the left lower extremity and shortly thereafter some vague lower abdominal discomfort. The patient's pain subsided and his subsequent course was uneventful until on the thirty-sixth day after hospital admission he experienced sudden chest pain, showed evidence of marked cyanosis, and rapidly expired. An autopsy was performed which revealed death to have been due to multiple pulmonary emboli. There had been a recent coronary arterial occlusion, but this had not involved the intima of the right heart, nor was there evident any other intracardiac source for these pulmonary emboli. On the contrary, there was a thrombosis in the left common iliac vein which might well have been the source of the patient's fatal emboli and preterminal clots in the mesenteric veins.

TABLE XIII. RELATIONSHIP OF FATAL PULMONARY EMBOLI TO THE USE OF POTENT DIURETICS ON THE MEDICAL SERVICE

YEARS	ADMISSIONS	DEATHS	DIURETIC USED (PER CENT)	PER CENT MORTALITY
1930-1935	6,024	5	20.0	0.083
1935-1940	6,343	6	16.0	0.093
Subtotal	12,367	11	18	0.089
POTENT MERCURIALS INTRODUCED AT ST. FRANCIS HOSPITAL				
1940-1945	11,399	10	50.0	0.088
1945-1950	12,360	24	53.0	0.211
1950-1953	7,400	24	44.0	0.324
Subtotal	31,159	58	51.0	0.186
Total	43,526	69	47.8	0.159

When multiple factors exist which predispose toward intravascular clotting, it is difficult to assign primary responsibility to any one factor. However, this case argues that too active dehydration therapy may well precipitate venous thrombosis, especially in a patient whose cardiovascular system and reserve have already been seriously damaged and who is hence disposed to thrombosis and fatal emboli.

THE SYMPTOMS OF PULMONARY EMBOLISM

Sudden occlusion of the pulmonary artery by an embolus causes pathologic, physiologic changes whose recognition makes possible the diagnosis of pulmonary embolism. Wolf[27] has briefly summarized these changes as follows: "The lodgment of a clot in a pulmonary artery produces local disturbances in pulmonary circulation, pulmonary hypertension, a lowering of systemic pressure, abnormal reflexes, and anoxia. The particular functional and structural alterations which

follow pulmonary embolism will depend on the proportionate role of these elements which are closely interrelated and upon the following factors: the caliber of the vessels occluded, the extent of propagation of the emboli within these vessels, and the pre-embolic state of the heart, lungs, and circulation.'' Because of these many variable factors, the diagnosis of pulmonary embolism is frequently difficult. For these reasons, then, a high index of suspicion that this complication may occur should be ever in one's mind when an untoward symptom presents itself in a patient presenting one of the factors predisposing to embolus which have been mentioned.

Table XIV lists the initial symptoms which we have encountered in our cases of pulmonary embolism. No symptom in itself is pathognomonic of pulmonary embolism. As may be noted, the outstanding symptom may at times appear to be more consistent with primary cardiac, cerebral, abdominal disease, or some other pulmonary condition rather than pulmonary embolism. Miller and Berry,[20] in their experience, believe that fewer than 15 per cent of their cases presented what might be called a typical textbook picture of pulmonary embolism, and yet they had a diagnostic accuracy of 42.3 per cent. Sulma[24] in a smaller series had an accuracy of 30 per cent. Our accuracy in the diagnosis of pulmonary embolism was 35 per cent. Our errors were attributable to diagnosis of acute cardiac failure in 28 cases, coronary occlusion in 14 cases, cerebrovascular accident in 8 cases, pneumonia in 4 cases, pericarditis in 1 case, and status asthmaticus in 1 case. Death was the first symptom in 7 cases, and in these instances, therefore, diagnosis was not recorded prior to autopsy. Were death not so rapid, it might be supposed that in many cases electrocardiography might be quite valuable in differential diagnosis. However, Carlotti and associates[9] advised that the findings of electrocardiographic signs of pulmonary embolism are essentially those of acute cor pulmonale and are not pathognomonic of pulmonary embolism alone. Even cor pulmonale was present in but 20 per cent of their cases. Similarly, Hampton and Castleman[15] have demonstrated that there are no x-ray findings which are diagnostic of pulmonary embolism. Hence, physical findings and their proper clinical evaluation still remain the mainstays of the accurate diagnosis of pulmonary embolism. The pulmonary vessels most frequently occluded in our experience are recorded in Table XV.

TABLE XIV. INITIAL SYMPTOMS IN 97 FATAL CASES OF PULMONARY EMBOLISM

SYMPTOM	NO. OF CASES	PER CENT INCIDENCE
Pulmonary		
Dyspnea	25	54.6
Chest pain	12	
Cyanosis	11	
Hemoptysis	5	
Systemic		
Sudden death	14	28.9
Shock	9	
Tachycardia	5	
Cerebral		
Restlessness	10	13.4
Disorientation	3	
Abdominal		
Nausea, vomiting	3	3.1
Total	97	100.0

Death after known pulmonary embolism took place within the first hour in 34 per cent of our cases and within the first twenty-four hours in an additional 39 per cent, and the remaining 27 per cent of the patients died during the

succeeding two to five days (see Table XVI). In general, the less pulmonary arterial obstruction, the longer the duration of survival (see Table XVII). However, some patients died when the embolus had eliminated only a relatively small proportion of aerating surface. This fact has been commented upon by De Takats and Jesser,[12] who have attributed these otherwise inexplicable fatalities to unfavorable autonomic reflexes affecting the heart, pulmonary tree, and the bronchi although, as previously noted, the size of the embolus and the pre-embolic status of the patient's heart and lungs are the fundamental factors in determination of the final outcome of small and moderate-sized pulmonary emboli.

TABLE XV. SITE OF OCCLUSION IN 97 FATAL CASES OF PULMONARY EMBOLISM

SITE OF OCCLUSION	NO. OF CASES	PER CENT INCIDENCE
I. 5 lobes (30 cases), right and left main pulmonary artery	34	35.1
II. 4 lobes (4 cases), artery to left lung plus 2 lobes,	4	7.2
artery to right lung plus lobe	3	
III. 3 lobes (14 cases), artery to left lung plus 1 lobe,	5	14.4
artery to right lung	9	
IV. 2 lobes (19 cases), artery to left lung,	2	19.6
artery to two lobes	17	
V. 1 lobe (23 cases), artery to one lobe	23	23.7
Total	97	100.0

TABLE XVI. PERIOD OF SURVIVAL AFTER PULMONARY EMBOLUS IN 97 FATAL CASES

SURVIVAL TIME (HR.)	NO. OF CASES	PER CENT DEAD
0-1	33	34.0
1-3	8	39.2
3-6	8	
6-12	8	
12-24	14	
24-48	13	26.8
48-120	13	
Total	97	100.0

TABLE XVII. ESTIMATED LOSS OF FUNCTIONAL CAPACITY IN 97 CASES OF FATAL PULMONARY EMBOLUS

ESTIMATED LOSS OF AERATING SURFACE (PER CENT)	NO. OF CASES	AVERAGE SURVIVAL TIME
75-100	25	3.26 hr.
50-75	15	7.85 hr.
25-50	32	2.10 days
0-25	25	5.80 days
Total or average	97	2.20 days

SUMMARY

1. The incidence of fatal pulmonary emboli has been increasing, its present incidence being 0.089 per cent of all hospital admissions and 5.0 per cent of all autopsies in our experience between 1950 and 1953.

2. The age group over 40 years accounts for 80 per cent of all fatal pulmonary emboli primarily because of the increased incidence of cardiovascular disease in this group.

3. Fatal pulmonary emboli occur most commonly on the medical, gynecologic, genitourinary, and general surgical services, in that order, and occur but rarely on the obstetrical service.

4. The most common conditions favoring pulmonary embolism are: cardiac disease, venous thrombosis, dehydration, and immobilization.

5. The heart was the site of origin in 52.8 per cent of all fatal cases of pulmonary emboli and was most common in arteriosclerotic heart disease, rheumatic heart disease, and coronary heart disease, in that order.

6. Of all fatal cases of pulmonary embolism, 64.7 per cent of patients had heart disease, and of these, 66.6 per cent were fibrillating; 20.6 per cent had a change in cardiac rhythm not long prior to embolization.

7. Venous thrombosis was the source of fatal pulmonary emboli in not more than 47.2 per cent of all cases, and of this group over one-half the thrombi had originated in the pelvis and possibly one-third had originated in the lower extremities.

8. Severe dehydration predisposes toward thrombosis and pulmonary embolism so that care should be taken to prevent excessive fluid losses or deficits in all patients.

9. The symptoms of pulmonary embolism are rarely typical and may suggest pulmonary, cardiac, cerebral, or abdominal disease.

10. Improvement in our ability to diagnose pulmonary embolism correctly at present must be based upon a high index of suspicion of its possibility, an adequate history, and a thorough physical examination if we are to better our present diagnostic accuracy of 30 to 40 per cent.

11. Since the heart is more frequently the source of pulmonary emboli than the veins of the pelvis or extremities, great care must be exercised to determine in which cases vena cava or iliac vein ligation will be of value in the prevention of pulmonary emboli.

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HISTOPATHOLOGIC CHANGES IN EXPERIMENTAL THERMAL WOUNDS

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THIS paper deals with progressive gross and histopathologic changes observed in various types of experimental burn wounds. An attempt is made to correlate these changes with degrees of heat penetration previously reported.[1] Subsequent communications will be concerned with bacteriologic aspects and the effects of dressings, antiseptics, antibiotics, débridement, and so forth upon the surface growth and invasion of microorganisms and upon ulceration.

Four sorts of burn have been studied: (1) low-temperature dry burn analogous to radiator, hot stove, or hot-water bottle burns, (2) live-steam scald, (3) alcohol flame char which reproduces fairly well the deep thermal injury from burning houses or clothes, and (4) flash burn from exploding aviation gasoline. Apparatus used to produce these burns has been described elsewhere.[1]

All our burns were small, being limited to circular areas 4 or 5 cm. in diameter. Narcotized dogs were used, although canine skin differs from human skin in certain important respects. The areas to be burned were clipped or shaved, and in some instances washed with soap and water, but were not treated with antiseptics. Some wounds were left exposed; others were dressed in various ways. Each animal received four to eight wounds, preferably on the back. The wounds, observed day by day, appeared to cause surprisingly little discomfort. No abnormal systemic effects were noted. Blood cultures remained sterile.

Gross characteristics of the burns are indicated in Table I and Fig. 1. Burns of each type were produced in a uniform manner. At appropriate intervals the animals were sacrificed and the burned areas were excised for study.

HISTOPATHOLOGY

Fig. 2 is a photomicrograph of a cross section of healthy canine skin taken from the abdomen. The epidermis, much thinner than that in human beings, is only two to four cells in thickness. The dermis, 1 to 3 mm. thick, composed largely of collagenous fibers, contains a great number of hair follicles and sebaceous glands and ducts, but no sweat glands. Beneath the dermis lies a layer of fatty tissue in a loose fibrous stroma.

1. *Low-Temperature Dry Burn.*—The histologic appearance of the skin twelve hours after a 70° C. dry burn is shown in Fig. 3. All of the structures appear essentially normal. Some surface keratin is being cast off. A few scattered collagen fibers stain less deeply than normally.

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Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

TABLE I. GROSS CHARACTERISTICS OF THE EXPERIMENTAL BURNS

SOURCE OF HEAT	TEMPERATURE AT SKIN SURFACE (° C.)	DURATION OF HEAT (SEC.)	GROSS APPEARANCE	
			IMMEDIATE	LATE
Hot metal	70	10	Normal	Ulceration in 4-6 days
		60	Normal	Ulceration in 3-4 days
Steam	95.5	2	Pale, inelastic, soggy	Ulceration in 3-4 days
		20	White, "lifeless," "cooked"	Ulceration in 2-4 days
Alcohol flame	About 750*	20	Brown char; skin leathery; surrounding zone of edema	Slow slough of eschar, beginning at edges, leaving large ulcer
Exploding gasoline vapor in oxygen	2,900	0.009	Singed hair (if any); no char	Healing without skin loss in many cases

*The alcohol flame tended to flicker. Actual measurements ranged from 670° to 820° C.

After two days, however, the epidermis is seen to have lost all cellular detail, although it remains an unbroken cover. The underlying dermis is edematous and disorganized; its collagen fibers show variable and abnormal staining, which suggests some sort of progressive chemical alteration. There is a moderate degree of lymphocytic infiltration. Epithelial degeneration extends to hair follicles and sebaceous glands deep in the dermis. In the subcutaneous fatty layer there are sheets of amorphous, pink-staining material suggesting coagulation or precipitated protein.

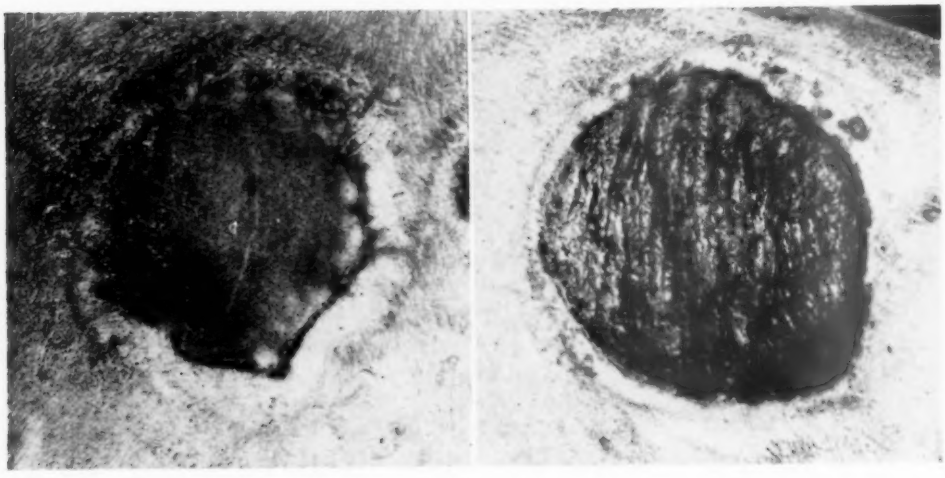
Fig. 4 shows the margin of a similar burn after four days. Toward the healthy side there is obvious hyperplasia and thickening of the epidermis; on the burn side all epithelium has disappeared, superficial necrosis is evident, and the presence of many leukocytes points toward bacterial invasion and local infection. To a limited extent, the inflammatory process involves the dermis on the healthy side also, undermining the epidermis. Blood vessels are dilated and full of blood.

The ulcerating center of this 4-day-old wound is shown in Fig. 5. The remains of a hair follicle may be seen on the left. All of the epidermis and much of the dermis have sloughed away, leaving a raw surface. The remaining collagenous tissue displays disordered architecture and varying degrees of destruction. Mingled with these fibers can be spotted an occasional young fibroblast. There is pronounced cellular infiltration, mostly leukocytes. Fig. 6, taken from the same slide, shows that the inflammatory process extends deeply into the subcutaneous tissues.

2. *Steam Scald.*—Fig. 7 is a photomicrograph of a live-steam scald of five seconds' duration. The biopsy was taken one hour after receipt of the injury. It is at once apparent that this type of burn produces far more severe immediate effects than the 70° C. dry burn. The epidermis is thrown into corrugations with complete loss of cellular structure. The dermis is a mass of amorphous coagulum. Epithelial cells of hair follicles and sebaceous ducts can no longer be made out clearly. The destruction extends through the entire thickness of the skin. There is some edema. The subcutaneous tissues look normal however.

The appearance two days later is similar but worse. No part of the skin remains viable. Hair follicles and glandular structures have degenerated completely. There is exfoliation of keratinized material, but the epidermal layer, although lifeless, is still intact as a covering and presumably remains an effective barrier to bacterial invasion. Destruction does not extend deeper than the dermis; subcutaneous tissues still appear healthy with only moderate small round-cell infiltration and engorgement of blood vessels.

After four days the scalded area has ulcerated. As Fig. 8 indicates, both epidermis and dermis have disappeared completely, leaving a surface of infected fat undergoing necrosis and slough. It is loaded with leukocytes. The inflammation, as Fig. 9 demonstrates, extends to and beyond the subcutaneous (panniculus carnosus) muscle.



A. *B.*

Fig. 1.—Gross appearance of an alcohol flame burn: *A*, on the third day, showing eschar and surrounding zone of edema and inflammation; *B*, on the eighth day, showing ulceration.

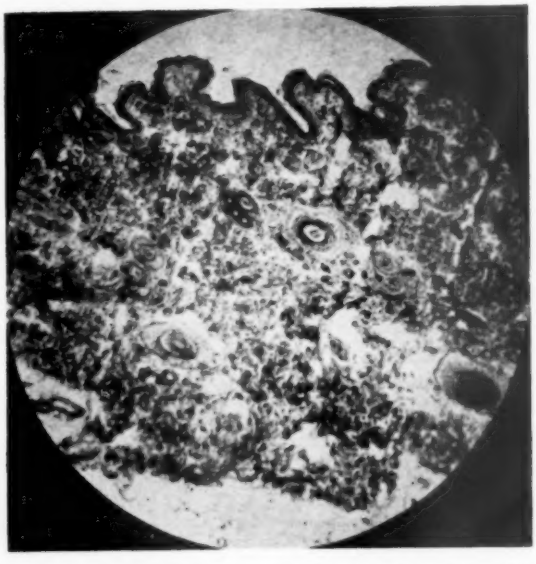


Fig. 2.—Cross section of normal canine skin of the abdomen. (×50; reduced ⅙.)

3. *Alcohol Flame Burn.*—A twenty-second alcohol flame burn produces a charred, leathery surface. There is prompt and striking contraction of the skin so that the burned area shrinks to about one-half its original size. Microscopic sections show that normal epidermis and dermis have been replaced by a wavy, amorphous coagulum, which takes a deep red color with trichrome

stain. No structural pattern remains. This eschar is less than one-half the thickness of the original skin. As far as one can tell microscopically, there is relatively little immediate change in the underlying fatty layer, but delayed

Fig. 3.

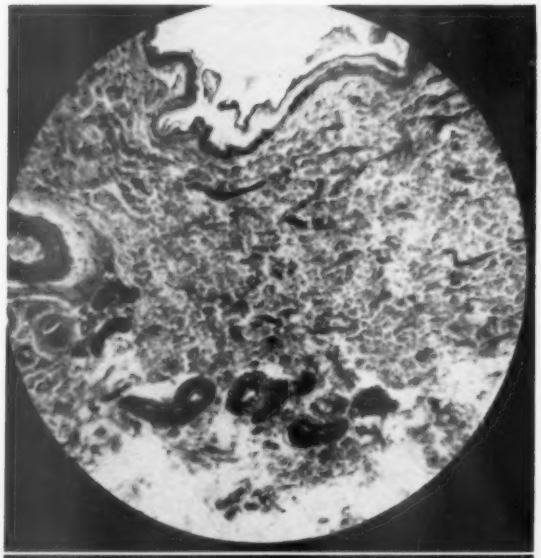


Fig. 4.

Fig. 3.—Histologic appearance of canine skin twelve hours after receipt of a 70° C. dry burn. (×50; reduced ⅙.)

Fig. 4.—Edge of a 4-day-old burn produced by a sixty-second contact with metal at 70° C. (×100; reduced ⅙.)

effects appear after three, four, or five days, similar to those described for the 70° C. contact burn and steam scald. Especially after the edges of the eschar begin to separate (Fig. 1, *A*), and infection spreads subcutaneously beneath the necrotic skin, do these changes become manifest.

4. *Flash Burn**.—Cross section of a flash burn one hour after the injury is depicted in Fig. 10. The changes, relatively slight as compared with the three preceding burns, appear to be limited to the epidermis and its immedi-

Fig. 5.

Fig. 6.

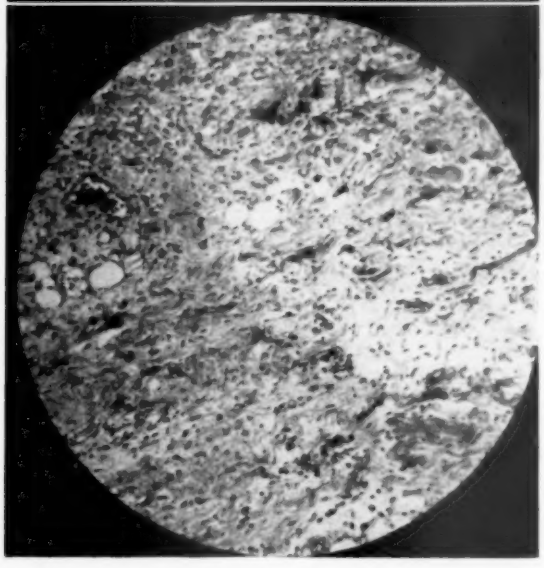


Fig. 5.—Ulcerating center of the burn of Fig. 4.
Fig. 6.—Dermal and subdermal tissues in the burn of Figs. 4 and 5.

ately underlying dermis. Superficial portions of follicles and ducts are damaged, but deeper structures seem to be normal.

Two days later, pathology is still limited to superficial portions of the skin. Occasionally one finds evidences in sections of a minor break in the

*It should be noted that these are thermal flash burns, not radiant burns, which penetrate more deeply.

epidermis and limited leukocytic infiltration (and presumably bacterial invasion) in the adjacent area. Intradermal epithelial appendages appear normal.

By the seventh day, the skin in most instances has returned to normal, grossly and microscopically (Fig. 11). The epidermal epithelium is thicker than usual, evidence that reparative activity has been present.

Fig. 7.

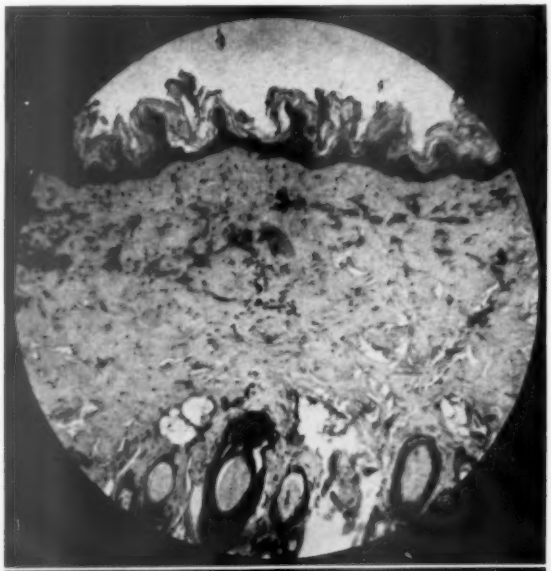


Fig. 8.

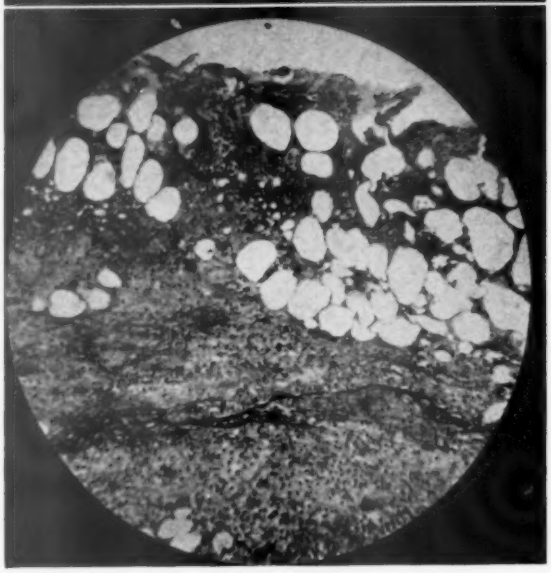


Fig. 7.—Histologic appearance of skin one hour after a five-second live-steam scald. (×100; reduced ⅙)

Fig. 8.—The acutely inflamed bed of an ulcerating wound; this followed a live-steam burn. (×100; reduced ⅙)

DISCUSSION

It is evident from study of microscopic sections that in these burns, destruction and reparative processes proceed concurrently. The earliest de-

tectable sign of repair, hyperplasia of epidermal cells at the periphery of the wound, is often seen within twenty-four hours after a burn. Granulation tissue, phagocytosis, fibroplasia, and recovery of individual cells appear later. On the other hand, cellular deterioration and necrosis, infection, abscess formation, and slough, are progressive, and usually do not reach a peak for several days following the trauma.

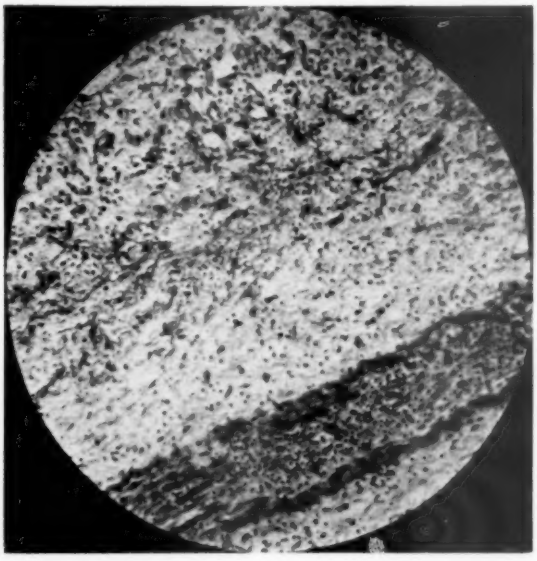


Fig. 9.—The burn of Fig. 8, showing extension of the acute inflammatory process into the subcutaneous tissue, to and beyond the panniculus carnosus muscle.

The effect of heat per se upon living cells and tissues is not clear. Actually, as our measurements have shown,[1] the amount of heat that penetrates into the deeper layers of the skin or into the subcutaneous tissues is surprisingly small, scarcely enough, one would think, to produce the extensive damage so obviously present in both clinical and experimental burn wounds. In relatively few of our burns did the temperature at a depth of 3 mm. or more below the skin surface exceed 50° C., and the duration of the heat wave was short. Yet these thermal injuries resulted in ulcerations many millimeters deep. Can it be that temperatures between 42° C. (maximum degree of fever compatible with life) and 50° C. (approximate temperature of a hot Japanese tub bath) are harmful to cutaneous and subcutaneous cells, and lead to their progressive deterioration and death? What is the mechanism of cellular injury? There is nothing in the histologic sections, as far as one can tell from staining and morphology, to suggest that this range of heating, lasting seconds, or at most one or two minutes, produces any sudden chemical change or distortion of cell architecture. Is the slower but ultimately lethal effect due to interference with the cell's metabolism, or its enzyme system, or some hypothetical vital principle in the nucleus? Or is it due to an external influence such as the production of or release of a hypothetical toxin? How important, in this regard, is the role of bacterial invasion and infection?

In pursuit of this problem, we cut squares of full-thickness skin from a dog's abdomen, using aseptic technique, immersed them in water baths at various temperatures for twenty seconds to ensure thorough heating of all the excised tissue, and then sewed the pieces of skin back in place. Results

Fig. 10.

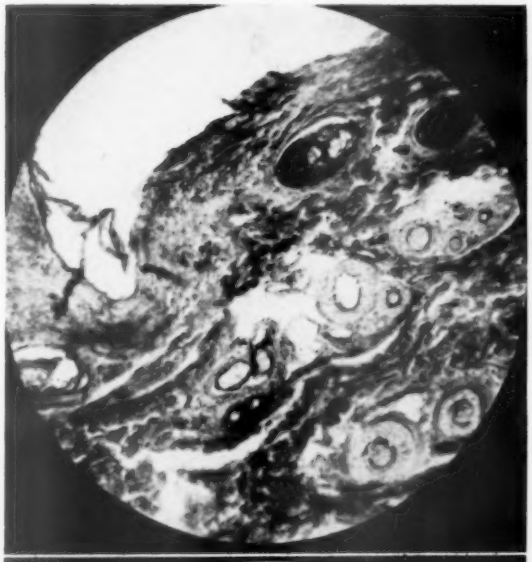


Fig. 11.

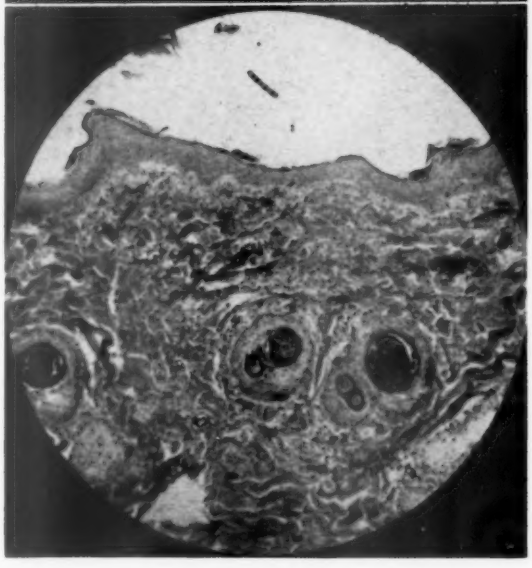


Fig. 10.—Section of skin one hour after exposure to a flash (gasoline explosion) burn. (×100; reduced ⅙.)

Fig. 11.—Healed skin seven days after a flash burn. (×100; reduced ⅙.)

of one such experiment are shown in Fig. 12. This is a severe test, for the excised skin is subjected not only to heat but also to operative trauma and temporary interruption of blood supply. But under the conditions of the ex-

periment, it is seen that minimal permanent tissue damage occurred at 40° C., whereas complete necrosis resulted when the tissue was heated to 50° C. Somewhat better results were obtained when the excised and heated skin was planted intra-abdominally on the peritoneal surface. Here the graft, heated to 50° C., survived in part, and all of its component parts could be seen histologically to be growing healthily.

We had previously been under the impression that extensive burns cause prompt coagulation or destruction of blood, and thrombosis of blood vessels, in the heated skin and subcutaneous tissues. We thought that this explained, at least in part, gradual breakdown of the wound and the pronounced reduction in total volume of circulating red cells which characteristically follows such injuries. But the discovery that relatively little heat actually penetrates into the skin and its underlying tissues threw doubt on that hypothesis. Further skepticism was aroused by failure to find many thrombosed vessels in our histologic preparations. These observations led us to a study of the effects of heat on blood itself.

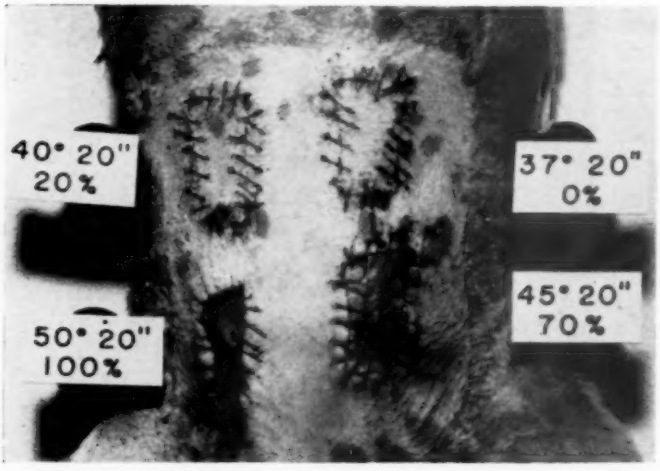


Fig. 12.—The effects of heat on transplanted skin (see text).

The action of heat on canine blood in vitro was studied. Under these artificial conditions, canine blood and blood elements show relatively little immediate change until temperatures are reached which far exceed those found in tissues in our experimental burns.

In this connection, the following experiment may be of significance. A dog's femoral artery and vein were connected by means of a long, slender polyethylene tube. This tube was then immersed in a water bath so that the flowing blood could be heated to any desired degree in transit and then be returned to the animal's general circulation. The rate of flow through the tube was regulated. The actual temperature of the blood in the tube as it left the water bath was measured by means of a thermocouple in the lumen. When no anticoagulant was used, the rapidly flowing blood could be raised to 55° C. without immediate clotting. When the animal was heparinized, it

was found that each unit volume of blood could be heated to 60° C. for from eight to forty-six seconds (in transit), and this process continued until (theoretically) the entire volume of circulating blood had passed through the plastic tube, without other symptoms than those caused by moderately increased body temperature. And if the heated blood was cooled again by passage through an ice bath before its return to the body, no symptoms of any sort ensued. There was no significant rise in the animal's white blood cell count, or other signs of toxicity. Hemolysis developed slowly. These animals survived and seemed to be none the worse for the experience. However, when high degrees of temperature were employed, such as boiling water in the bath with no attempt at recooling, the animals soon developed hyperpyrexia, severe dyspnea, and convulsions, and died. In view of these observations, we question whether heating of "trapped" blood per se in burn wounds is an important factor, either in progressive deterioration of the injured tissues or in the development of postburn anemia. They remain unsolved problems.

An important observation, in our opinion, is that the epidermis, however badly damaged by heat, seems to remain an effective barrier to bacterial invasion as long as the surface is unbroken. The coincidence of histologic evidence of infection in the dermis and subdermal tissues, and of rapid deterioration and ulceration of the wound on the third, fourth, or fifth days, strongly suggests an etiological relationship. This aspect of the problem, which has important practical implications, has been the subject of intensive study. Our findings and conclusions in that regard do not fall within the scope of the present discussion, however, and will be reserved for future reports.

SUMMARY

Four types of experimental burn have been studied. In creating the burns, an effort was made to reproduce the sorts of thermal injury most commonly seen clinically.

Gross and histopathologic characteristics of these experimental burns are described. The most severe injuries were caused by steam and flame burns, the least severe by gasoline explosion flash burns.

In addition to immediate tissue damage, thermal trauma appeared to initiate, at levels too deep to be reached by destructive amounts of heat, progressive cellular deterioration that resulted finally in extensive necrosis and ulceration. The nature of that destructive process is not well understood.

In burn wounds, the processes of destruction and repair appeared to coincide and be competitive.

It is doubtful whether the primary effect of heat on blood "trapped" in the burned areas was an important factor, either in delayed death of local tissues or in the production of postburn anemia.

A finding of possible importance is that burned epidermis, as long as it remained an unbroken surface, seemed to serve as an effective barrier against bacterial invasion.

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DISCUSSION

DR. EDWARD L. HOWES (New York, N. Y.).—I would like to congratulate Dr. Price on carrying out fundamental work on burns. Few things bore surgeons more than the fundamental processes involved in the healing of burns.

I want to call attention to one thing—the difficulty of assessing death of some tissues by means of histologic staining. Stained tissues are dead and therefore they must undergo some change in chemistry before the animal is killed to get differences in tinctorial response. Notoriously, collagenous tissues undergo change very, very slowly after death, so that it is not surprising that the derma shows very little change by the second or third day after partial burning.

However, you can challenge burned collagen by means of enzymes to prove denaturization has taken place. They become susceptible to the action of trypsin. When this is done you will find, to your surprise, great variations in changes with any one temperature. In any one section of dermis, there are fibers that are thoroughly denatured and can be attacked by a trypsinlike enzyme and fibers directly adjacent that cannot be dissolved by means of trypsin because they are not sufficiently denatured. Ultimately however, in the course of two weeks, denaturization of all takes place.

Dr. Price should be heartily congratulated in blasting the assumption that the surface of the burn is relatively free of bacteria. I think that this is scientific nonsense. The bacteria are still in the hair follicles of the partially burned tissues where an infection can be produced.

THE ETIOLOGY OF "MEAT INTOXICATION" IN THE ECK FISTULA DOG

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INTEREST in the physiologic effects of a portacaval shunt can be traced directly to the report in 1877 of Nikolai Eck,[1] in which he described the successful completion of such an anastomosis in the dog. It was not until sixteen years later that Pavlov and his associates[2] referred to the neurological symptoms which occurred in such dogs and which followed the ingestion of meat. A more complete description of this condition, which is called "meat intoxication," was given by Baló and Korpássy,[3] who specified the following symptoms: lethargy, weakness, excessive salivation, hypotonia, ataxia, amaurosis, stupor, coma, convulsions, and sometimes death.

One of the major difficulties in studying this syndrome has been the inconstancy of the appearance of the symptoms. Not all dogs with Eck fistulas develop intoxication when fed on meat.[3-6] Svec and Freeman,[7] by force-feeding the dogs which refused to eat meat, were able to produce symptoms in eleven of thirteen dogs, eight of which died.

The sustained interest in the syndrome of "meat intoxication" has not helped to clarify the factors causing the symptoms. Attention has been focused on substances which might be absorbed into the portal circulation and, because of the Eck fistula, by-pass the liver to enter the general circulation. Pavlov[2] thought that carbamic acid was the toxic agent. Other workers suggested guanidine,[8] amino acids,[7] unknown "toxins,"[9] and even virus infections of the central nervous system.[10] Several investigators[2, 4, 11, 12] observed that ammonia levels were abnormally high in "meat intoxication" and suggested that ammonia poisoning might be the cause of this condition. None of these suggestions has been substantiated however, and the most recent reviews of the problem stated that the etiology of "meat intoxication" was unknown.

In a human patient with an Eck fistula, central nervous system symptoms caused by ammonia intoxication have followed the ingestion of protein and other substances which may yield ammonia.[13] Certain nitrogenous substances have precipitated a comatose state in patients with cirrhosis.[14]

It was with these facts in mind that the following investigations of ammonia metabolism in Eck fistula dogs were carried out.

METHODS

Eck fistulas were constructed in nineteen healthy adult mongrel dogs weighing between 10 and 20 kilograms. Intravenous veterinary Nembutal was used as the anesthetic agent.

These studies were supported by grants from the Atomic Energy Commission and the United States Public Health Service.

Read at the meeting of the Society of University Surgeons, Rochester, New York, Feb. 11-13, 1954.

*Bilton-Pollard Travelling Fellow of University College Hospital, London.

The operation was performed through a right subcostal incision extending from the xiphoid process to the lateral edge of the erector spinae muscles. The hepatorenal ligament was divided to allow the liver to be retracted upward under the costal margin and the kidney to be displaced downward. The duodenum was rotated to the left to expose the portal vein. The mesentery over the portal vein was incised, and the vein dissected free from its bed. The lumen of the inferior vena cava was partially occluded with a Satinsky clamp, and an ellipse of vein wall 1 cm. in length was excised. The portal vein was ligated at the hilum of the liver and occluded at its mesenteric end by a Blalock clamp. A longitudinal incision was made in the side of the portal vein opposite the opening in the vena cava, and the anastomosis was completed with a continuous everting mattress suture of 00000 braided arterial silk. In order to be certain that recanalization would not occur, the portal vein was transected between ligatures at the hilum of the liver. The incision was closed in layers with silk sutures. Postoperatively the dogs were starved for twelve hours and then given a standard diet of dog biscuit and milk.

Horse meat was used as the initial agent for producing "meat intoxication." In accordance with the observations of other investigators in this field, it was found to be extremely difficult to induce attacks consistently by meat-feeding. The dogs would either refuse to eat more than small amounts of meat from the beginning or at the onset of very mild symptoms, would refuse meat entirely. To induce attacks of "meat intoxication" which could be observed closely and coordinated with serial determinations of peripheral blood ammonia, it was necessary to force-feed horse meat in divided feedings to a total of 1,000 to 1,500 Gm. daily. (All five dogs handled in this fashion developed "meat intoxication" and among them had ten attacks.)

Urea was administered in total dosages of 60 to 75 Gm. by mixing it with the standard diet.

Ammonium salts were found to be unsatisfactory for inducing this syndrome because ingestion or tube-feeding of sufficient amounts (10 to 12 Gm. a dose) resulted in severe and protracted vomiting.

The urease utilized in these experiments was a partially purified extract of jack bean flour with an activity of approximately 2,000 units per gram. The powder was dissolved in distilled water (50 units per milliliter) immediately before use and given by intravenous injection in doses of 25 to 75 units.

The blood ammonia concentration was determined on 1 ml. samples of peripheral venous blood by a previously reported modification[13] of the microdiffusion technique described by Conway.[15] The results are expressed in micrograms of ammonia nitrogen per 100 ml. of whole blood. By this method the normal range of blood ammonia, as measured in fifteen normal dogs, was 49.8 to 76.0 μg per cent of ammonia nitrogen with a mean of 58.4.

RESULTS

Eck fistulas were constructed in nineteen dogs, of which six died as a result of the operation and two were considered unsatisfactory for experimental purposes. Eleven dogs remained. Of these eleven dogs, all, at one time or another, showed signs of "meat intoxication." The episodes varied in degree, ranging from mild behavior changes to severe attacks terminating in convulsions, coma, and death. In all, twenty attacks were observed; the findings are summarized in Table I.

The symptoms of "meat intoxication" varied with the individual dog, but the over-all pattern has been relatively constant. The dogs, which were kept in individual cages, were normally boisterous and barked freely when released. At the onset of an attack, a dog would become quiet, reluctant to leave his cage, refuse feedings, and would not jump up at the attendant. Often a dog would be anxious to return to his cage. As the symptoms progressed,

ataxic and rotary movements appeared, at first brought on only by exercise but later in evidence continuously. When ataxia was severe, the dog became blind and would wander aimlessly about the room until he collided with an object; he would then remain motionless with his head resting against it. At this stage, the dog was unresponsive to painful stimuli, and the corneal reflex became absent. If the syndrome progressed to a terminal stage, convulsions, coma, and death ensued. In one dog, however, two isolated convulsions complicated an otherwise mild and transient attack.

Detailed studies of blood ammonia levels during episodes of "meat intoxication" are shown in Figs. 1 through 6. It is apparent that there is a con-

TABLE I. SUMMARY OF ATTACKS OF "MEAT INTOXICATION" IN THE ECK FISTULA DOGS

DOG	NO. OF ATTACKS	DURATION (HR.)	DESCRIPTION OF ATTACK	PRECIPITATING FACTORS	RISE IN AMMONIA LEVELS DURING ATTACKS*	REMARKS
1	1	72	Ataxia amaurosis, hypesthesia	Not known	375-402	Ammonia level not determined until 30 hours after onset of attack
2	3	72	Ataxia	Fermented food	84-348	
		4	Quiet, vomiting	Ammonium citrate 8 Gm.	160-951	Duration of "sharp rise" less than 1 hour
		24	Coma and death	Urea 75 Gm.	83-2,405	
3	2	24	Quiet, mild ataxia	Fermented food	325-815	
		4	Quiet and uninterested in surroundings	Ammonium citrate 4 Gm.	441-1,267	Vomited and level fell rapidly to subtoxic levels
5	1	12	Coma and death	Meat	———	Died suddenly in night after eating small amounts (300-400 Gm.) meat for 4 days
7	4	72	Ataxia and amaurosis	Meat 3 days	241-676	
		50	Ataxia and amaurosis	Meat 2 days	266-855	
		50	Ataxia only	Meat 1 day	354-550	
		72	Coma and death	Meat 2 days	110-995	
8	1	24	Coma and death	Urea 60 Gm.	171-758	
11	3	48	Ataxia, 2 convulsions	Meat 4 days	101-383	
		96	Ataxia	Meat 3 days	118-455	
		20	Mild ataxia and hypesthesia	Urease (125 units	80-595	
15	1	40	Convulsions, coma, and death	Meat 2 days	143-1,576	
16	1	55	Convulsions, coma, and death	Meat 3 days	128-489	
17	2	12	Mild ataxia	Meat 4 days	72-387	
		30	Coma and death	Meat 2 days	118-492	
19	1	7	Ataxia	Urease (175 units)	137-743	

*Ammonia levels measured in micrograms NH_3–N per cent. Range in normal dogs was 49.8–76.0 (μg) per cent.

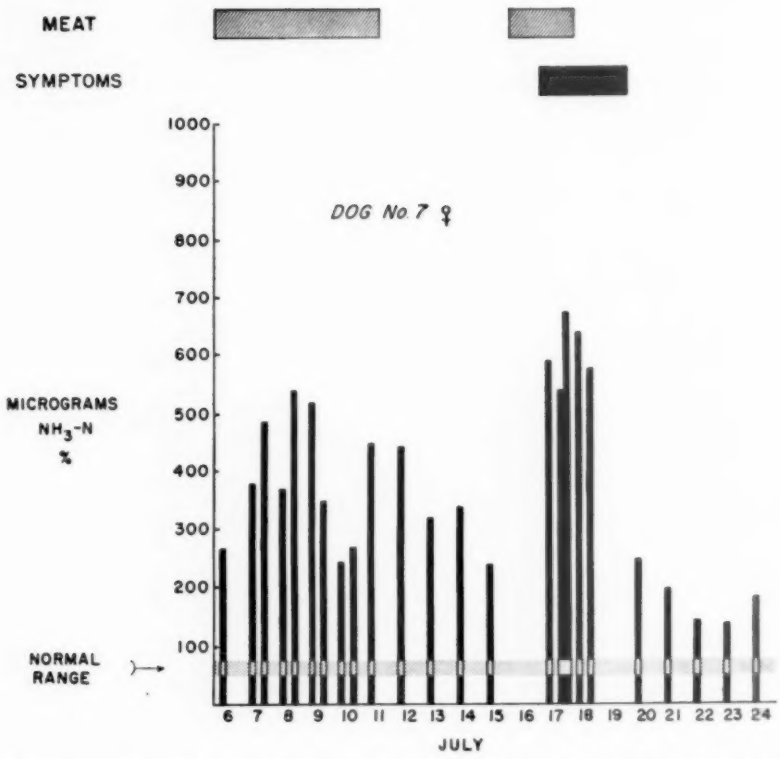

Fig. 1.—The effect on an Eck fistula dog of meat feeding. Symptoms did not occur during the first experiment when the blood ammonia level did not rise above 550 (μg) per cent.

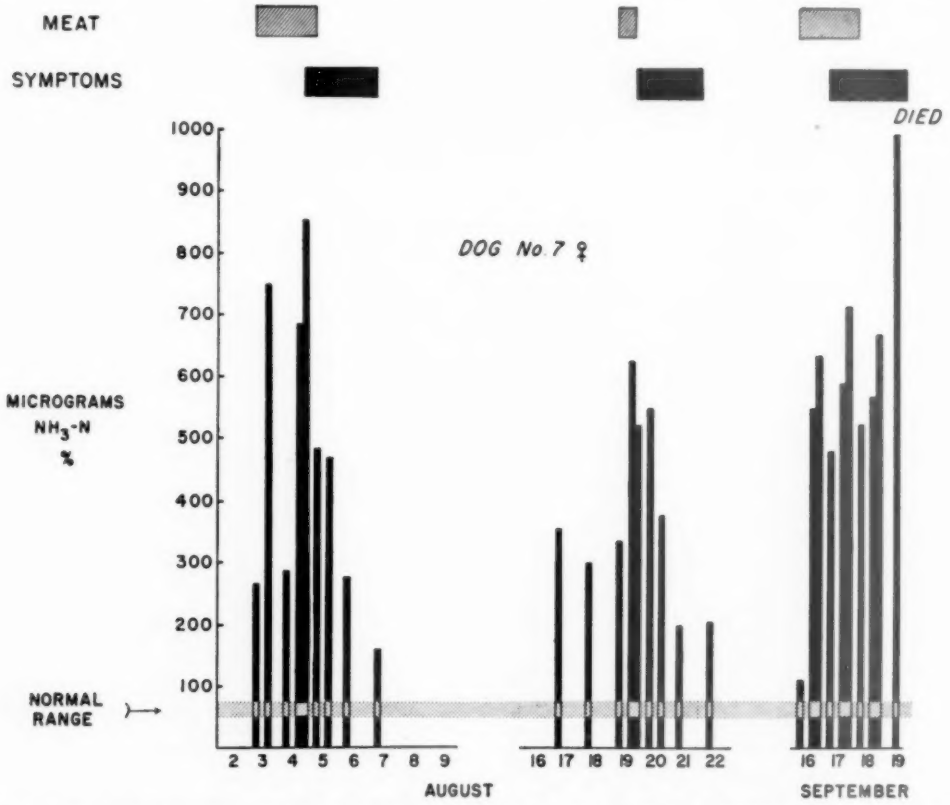

Fig. 2.—The effect on an Eck fistula dog of meat feeding. Three distinct attacks of "meat intoxication" were induced with concomitant rises in the level of blood ammonia.

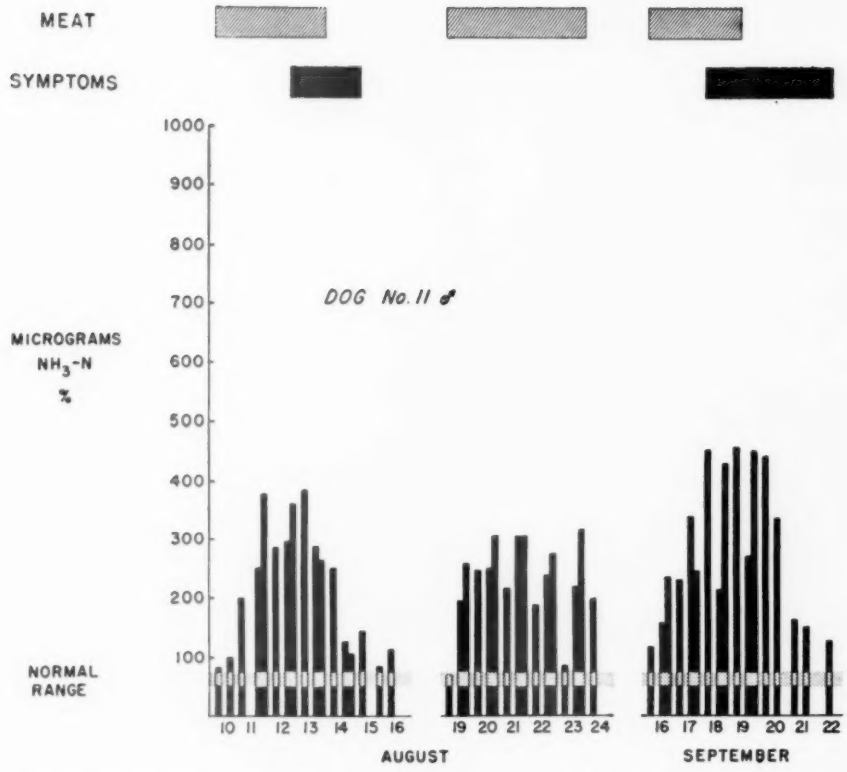

Fig. 3.—The effect on an Eck fistula dog of meat feeding. Again symptoms did not occur in this animal until the blood ammonia rose to a critical level.

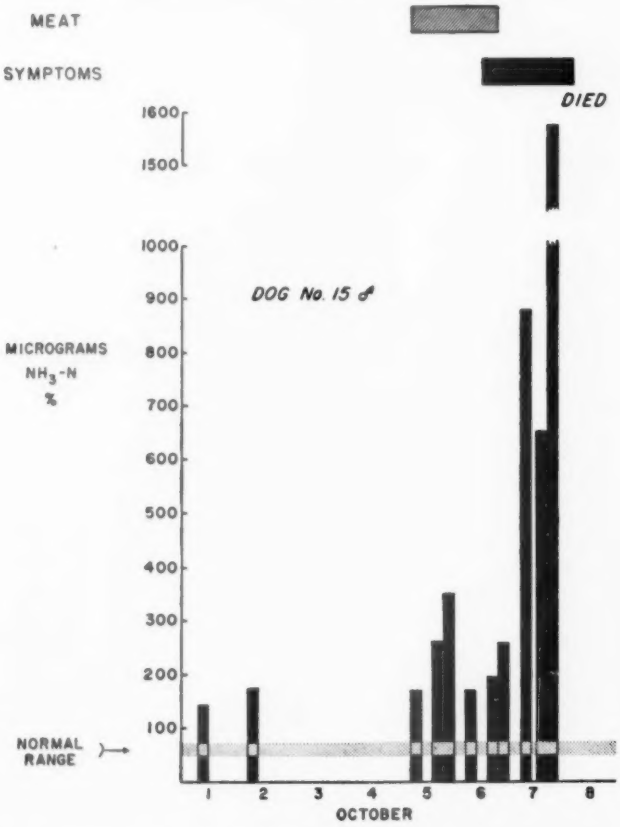

Fig. 4.—A single fatal attack of "meat intoxication" in another Eck fistula dog.

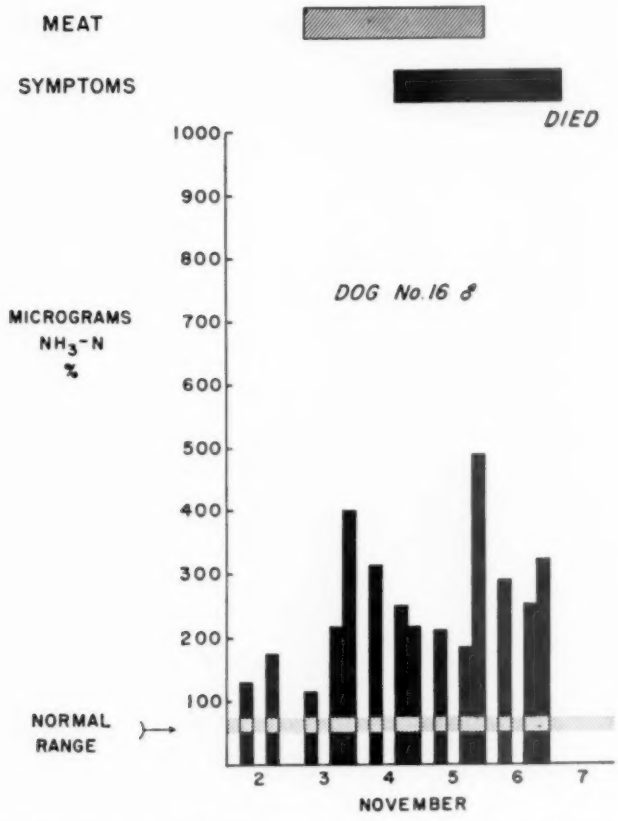

Fig. 5.—Another example of fatal "meat intoxication" in an Eck fistula dog.

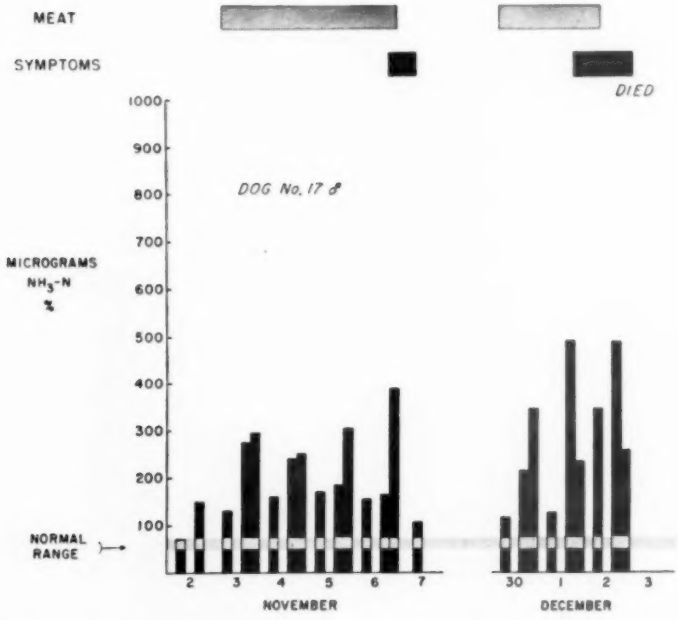

Fig. 6.—The effect of an Eck fistula dog of meat feeding in producing a transient and then a fatal attack of "meat intoxication."

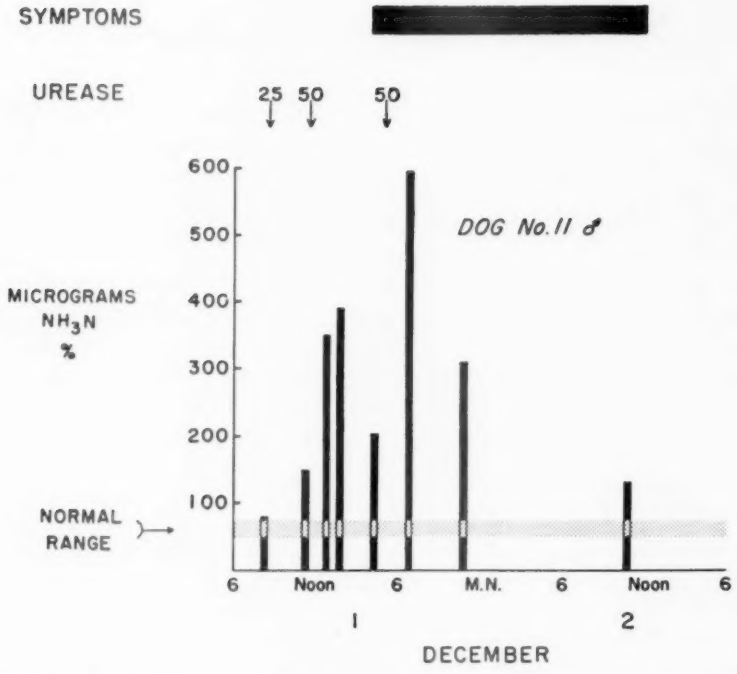

Fig. 7.—The effect on an Eck fistula dog of intravenous urease. "Intoxication" occurred which was identical in symptoms and concomitant blood ammonia elevations to "meat intoxication."

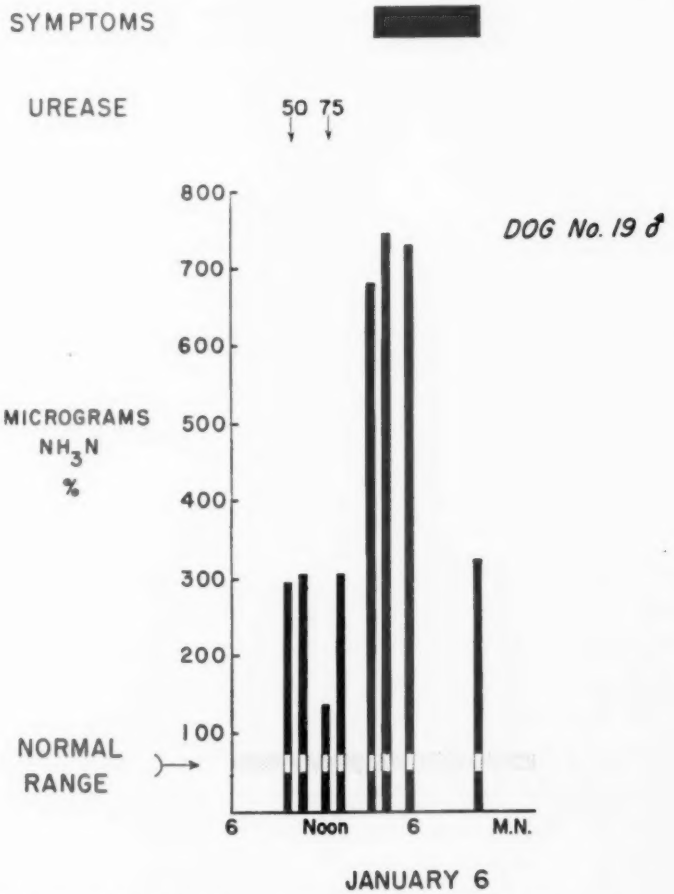

Fig. 8.—The effect on an Eck fistula dog of intravenous urease. "Intoxication" occurred which was identical in symptoms and concomitant blood ammonia elevations to "meat intoxication."

sistent and considerable rise in the blood ammonia with the onset of each attack; however, the symptoms may persist for some hours after the blood ammonia has fallen to previous levels. The concentration of blood ammonia at which symptoms appear shows considerable individual variation, but in dogs Nos. 7 and 11, in which only mild attacks were induced, the ammonia concentration at which symptoms appeared was about two and one-half times the average daily maximum on a low-protein diet (Figs. 1, 2, and 3). (Even on a restricted protein intake, Eck fistula dogs will run a moderately elevated blood ammonia level.) In order to induce attacks, a high level must be sustained for several hours; transient high peaks in ammonia concentration are not usually followed by neurological symptoms. In Figs. 1 and 3, it is important to note that the feeding of meat did not cause "intoxication," unless critical levels of blood ammonia were attained. The experiments represented by Figs. 4, 5, and 6 demonstrate that this "intoxication" can be lethal.

The administration of urea has been effective in producing attacks identical to "meat intoxication" and associated with the same pattern of elevation in the blood ammonia. In two dogs (Nos. 2 and 8, Table I), the inclusion of a total dosage of 60 to 75 Gm. of urea in their diet over a period of one to two days led to death; in one instance the terminal level of ammonia was 2,405 μg per cent and in the other 758 μg per cent.

On the other hand, the administration of ammonium salts has not been so successful. Elevated ammonia levels of very short duration have been produced and have been accompanied by mild symptoms, but severe vomiting invariably prevented the animals from retaining the administered salts.

The results of the intravenous administration of urease were important, inasmuch as they demonstrate that elevated ammonia levels and attendant neurological symptoms can be produced without the oral administration of nitrogenous substances. Repeated small (25 to 75 units) injections of urease were given to two dogs (Nos. 11 and 19). The results of these experiments are shown in Figs. 7 and 8. When the ammonia concentration was maintained at two to three times the average pretreatment maximum, the pattern of mild "meat intoxication" with ataxia appeared. In dog No. 11, symptoms and ammonia levels were comparable to those of a previous attack induced by meat (Figs. 3 and 7). It should also be pointed out that the injection of urease was not accompanied by any toxic symptoms unless critical elevations in blood ammonia ensued (Figs. 7 and 8).

DISCUSSION

It is apparent from these investigations that "meat intoxication" in Eck fistula dogs is a distinct, reproducible, and sometimes fatal syndrome. It is also apparent that the ingestion of other nitrogenous substances will cause the same symptoms and that regardless of the agent which precipitates the symptoms, a distinct elevation in the concentration of peripheral blood ammonia is a constant accompaniment of the onset of the syndrome. Serial determinations of blood ammonia levels are important in establishing this correlation because levels may fall many hours before the symptoms disappear.

As further evidence that ammonia is the etiological factor in this syndrome, intravenous urease was observed to cause identical symptoms but only if given in amounts sufficient to bring about considerable and sustained rises in ammonia concentration.

The rationale for the association of this biochemical disturbance with an Eck fistula is clear. It has been established that the level of ammonia concentration in the portal vein of the dog is considerably higher than in the peripheral blood.[2, 16] Dinsis and Hastings[17] have demonstrated the urea-splitting capacity of microorganisms in the gastrointestinal tract. The ornithine cycle for synthesis of ammonia to urea in the liver[18] is well accepted. Therefore, under conditions of excessive intake of nitrogenous substances from which ammonia may be liberated, the existence of an Eck fistula could facilitate the accumulation of toxic levels of ammonia in the blood.

The importance of these observations on the Eck fistula dog is related to the increasing frequency with which operations designed to shunt portal blood into the systemic circulation are being employed in man, either for the relief of portal hypertension or attendant upon resection of the portal vein for pancreaticoduodenal cancer. Initial observations on ammonia intoxication in man have been reported,[13] and further studies are in progress.

SUMMARY AND CONCLUSIONS

1. The symptoms of "meat intoxication" in the dog constitute a distinct and reproducible syndrome.

2. The central nervous system disturbances may be induced by the oral administration of meat, urea, or ammonium salts or by the intravenous injection of urease. In all cases, the onset of symptoms was accompanied by a considerable and sustained rise in the concentration of ammonia in the peripheral blood.

3. The rationale for this concept of ammonia intoxication in the Eck fistula dog and the implications with respect to surgery of the portal system in man are discussed.

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DISCUSSION

DR. WILLIAM E. ABBOTT (Cleveland, Ohio).—The observations of Dr. McDermott and his group are very interesting, especially if one attempts to correlate his findings with what we encounter clinically. About ten years ago, when we were studying patients who had had a thermal injury, we force-fed them employing a very high-protein diet. We noted that when very high-protein feedings were started shortly after a moderate or severe burn, the patient often became confused and toxic. In an attempt to simulate these results, we produced an experimental burn involving 40 per cent of the body surface of animals and, by giving high-protein feedings by stomach tube, we obtained animals, which normally would have survived such an injury, which were in an extremely serious state. At that time, we appreciated the fact that the early institution of very high-protein diets begun within one or two days after a burn was often poorly tolerated, but did not realize that high blood ammonia levels might account for the toxicity.

More recently, we have seen "hepatic coma" in cirrhotic patients who have been given moderately high-protein diets along with cation-exchange resins. In some patients of this type, the mental confusion may have resulted from water intoxication (hyponatremia with overhydration), but it has also occurred in some cirrhotic patients in whom we have given resins high in ammonia, hoping to exchange the latter ion for sodium. In such a situation, the mental confusion and coma have been alleviated by stopping the resin. While further clarification is needed to differentiate the various causes and therapy of coma, I feel that the observations of Dr. McDermott and his associates will help to elucidate the problem and will have more clinical significance than most of us realize.

DR. McDERMOTT (closing).—I would like to thank Dr. Abbott for his discussion. His observations are extremely interesting. We have studied approximately 100 patients with disturbances of ammonia metabolism, patients with portacaval shunts, and a large number with cirrhosis in various phases of decompensation. We have observed the symptoms Dr. Abbott described. The role of ammonia intoxication is not entirely clear, but in a number of cases this may be the important cause of the syndrome. We now think we can correlate it with electroencephalographic and histopathologic changes in the brain.

Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS FEB. 11-13, 1954, ROCHESTER, N. Y.

KEITH S. GRIMSON, M.D., DURHAM, N. C.

THE fifteenth annual meeting of the Society of University Surgeons was held in Rochester, New York, the site of its first meeting. This fifteenth meeting was held on Feb. 11, 12, and 13, 1954. The Society was the guest of the University of Rochester School of Medicine and Dentistry. Dr. W. J. Merle Scott, acting chairman of the Department of Surgery, read a message from Dr. John J. Morton, emeritus. Dr. Morton was in Japan on official business. Dr. Herman E. Pearse, chairman, was not able to take an active part in the proceedings. Welcoming remarks were extended by Dr. Donald Anderson, dean. The program for Thursday, February 11, was arranged by the faculty of the School of Medicine and was appropriately presented in their George H. Whipple Auditorium. Dr. W. J. Merle Scott and Dr. W. Andrew Dale were chairmen of the morning program. Subjects and authors were as follows:

1. Inflammation and Body Metabolism—Dr. G. H. Whipple
2. Tumor Host Relationships: Study of Appetite Factors—Dr. M. Radakovich
3. The Relation of Body Sodium and Rental Function—Dr. J. Schlegel
4. Esophagoplasty With Intrathoracic Colon—Dr. C. D. Sherman, Jr., and Dr. E. B. Mahoney
5. Air Pressure Treatment of Resistant Stasis Ulcers—Dr. W. J. Merle Scott
6. A Study of the Carcinogenic Effect of Beta-Naphthylamine on Normal Bladder and Substituted Isolated Sigmoid Loop Bladder of Dogs—Dr. H. Boyd, and Dr. W. W. Scott
7. Newer Studies of Dog Blood Groups—Dr. S. N. Swisher, Dr. G. Miller, and Dr. L. E. Young
8. Relationships of Host Cell Growth and Viral Proliferation—Dr. H. R. Morgan
9. Surgical Treatment of Hypospadias—Dr. R. M. McCormack

The Society adjourned for lunch as guest of Strong Memorial Hospital at Helen Wood Hall. Dr. Harry D. Kingsley and Dr. Charles D. Sherman, Jr., then presided over the afternoon program in the Whipple Auditorium. Subjects and authors were as follows:

1. The Treatment of Scoliosis—Dr. L. Goldstein
2. An Experimental Study of Flash Burns—Dr. H. D. Kingsley, and Dr. H. E. Pearse
3. Pulmonary Ventillation and Blood Flow Relations—Dr. H. Rahn
4. Preoperative and Postoperative Cardiodynamic Studies on Patients Having Mitral Commissurotomy—Dr. P. N. G. Yu, Dr. F. Lovejoy, Dr. H. Joos, and Dr. R. Nye
5. Regional Heparinization: An Experimental Study—Mr. D. A. Ohlwiler
6. The Use of Plastics to Reinforce Vein Grafts Replacing Large Arteries—Dr. W. A. Southgate, Dr. J. J. Fomon, and Dr. E. B. Mahoney
7. Ligation of the Vena Cava: An Experimental Study—Dr. W. A. Dale, Dr. F. Pualwan, and Dr. Stephen Bruney
8. Demonstration of Cine-Fluorography—Dr. C. Sherwood, Dr. G. Ramsey, Mr. S. Weinberg, and Dr. S. Watson

Papers by members of the Society were presented during the second and third days of the meeting. All papers and discussions are published in this number of SURGERY.

Book Reviews

Atlas of Orthopaedic Traction Procedures. By Carlo Scuderi, B.S., M.D., M.S., Ph.D. Pp. 230, with 124 illustrations. St. Louis, 1954, The C. V. Mosby Company, $12.50.

In this manual Dr. Scuderi, who has a wealth of practical experience from which to draw, has completely covered all types of traction and traction devices which are accepted for use today.

The illustrations are excellent and the text clear and concise. This is a particularly valuable book for residents who are beginning their orthopedic careers, and I believe it includes information which is covered only incompletely in other texts. I think orthopedic surgeons and others who deal with traumatic injuries will find it a very useful volume.

Atlas of Operative Technics—Anus, Rectum, and Colon. By Harry E. Bacon and Stuart T. Ross. Pp. 301, with 403 illustrations. St. Louis, 1954, The C. V. Mosby Company.

This is an excellent surgical atlas of the anus, rectum, and colon. With the evolution of surgery of the colon and anorectum, this book fulfills a very vital need. It emphasizes technical details of operative procedures that are difficult to describe accurately in textbooks or to see while watching an actual operation.

Surgery of the colon, rectum, or anal canal has become more universal in recent years. It has become more complex, thus making a book of this type essential and valuable.

This atlas, by two surgeons of the experience and skill of Dr. Bacon and Dr. Ross, is a helpful and valuable addition to the library of the general surgeon, as well as that of the proctologist.